



ESTIMATION OF THE INFECTION RATE IN EPIDEMIC MODELS WITH MULTIPLE POPULATIONS

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Cover image: spread of the Black Death pandemic in Europe (1347–1351).

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Abstract

The effect of infectious diseases on human development throughout history is well established, and investigation on the causes of infectious epidemics – and plagues in particular – dates back at least to Hippocrates, the father of Western medicine. The mechanisms by which diseases spread, however, could not be fully understood until the late nineteenth century, with the discovery of microorganisms and the understanding of their role as infectious agents. Eventually, at the turn of the twentieth century, the foundations of the mathematical epidemiology of infectious diseases were laid by the seminal work of En'ko, Ross, and Kermack and McKendrick.

More recently, the application of graph theory to epidemiology has given rise to models that consider the spread of diseases not only at the level of individuals belonging to a single population (population models), but also in systems with multiple populations linked by a transportation network (meta-population models). The aim of meta-populations models is to understand how movement of individuals between populations generates the geographical spread of diseases, a challenging goal whose importance is all the greater now that long-range displacements are facilitated by inexpensive air travel possibilities.

A problem of particular interest in all epidemic models is the estimation of parameters from sparse and inaccurate real-world data, especially the so-called infection rate, whose estimation cannot be carried out directly through clinical observation. Focusing on meta-population models, in this thesis we introduce a new estimation method for this crucial parameter that is able to accurately infer it from the arrival times of the first infective individual in each population. Moreover, we test our method and its accuracy by means of computer simulations.

Keywords: mathematical epidemiology of infectious diseases, meta-population models, infection rate estimation.

Resumo

A influência das doenças infecciosas no desenvolvimento humano ao longo da história está bem estabelecida, e a investigação sobre as causas das epidemias infecciosas – especialmente as pragas – remonta pelo menos a Hipócrates, o pai da Medicina ocidental. Os mecanismos de difusão das doenças, no entanto, não podiam ser totalmente compreendidos até o final do século XIX, com a descoberta dos microrganismos e a compreensão do papel deles como agentes infecciosos. Finalmente, na entrada do século XX, os fundamentos da epidemiologia matemática de doenças infecciosas foram assentes pelas obras seminais de En'ko, Ross, e Kermack e McKendrick.

Mais recentemente, a aplicação da teoria dos grafos à epidemiologia tem dado origem a modelos que consideram a propagação das doenças não só ao nível de indivíduos pertencentes a uma única população (modelos de população), mas também em sistemas com múltiplas populações ligadas por uma rede de transportes (modelos de meta-população). O objectivo dos modelos de meta-população é entender como é que o movimento de indivíduos entre as populações determina a distribuição geográfica das doenças, um desafio cuja importância é ainda maior hoje em dia, sendo os deslocamentos de longo alcance facilitados pela possibilidade de viagens aéreas económicas.

Um problema de particular interesse em todos os modelos epidémicos é a estimação dos seus parâmetros a partir de dados reais esparsos e imprecisos, especialmente a chamada taxa de infecção, cujo valor não pode ser determinado directamente através da observação clínica. Focando a atenção nos modelos de meta-população, nesta tese apresentamos um novo método de estimação para este parâmetro crucial que o infere com precisão a partir dos tempos de chegada do primeiro indivíduo infeccioso a cada população. Adicionalmente, testamos o nosso método e a sua precisão recorrendo a simulações computacionais.

Palavras chave: epidemiologia matemática das doenças infecciosas, modelos de meta-população, estimação da taxa de infecção.

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CHAPTER 1

Introduction and motivation

Throughout history, infectious diseases have profoundly affected human development: for example, the Black Death (bubonic plague) that swept Europe in several waves during the fourteenth century is estimated to have caused the death of as much as one-third of the European population, recurring regularly for more than three centuries [9]. The defeat of the Aztecs and Incas by invading Spaniards in 1519 and 1532, respectively, can also be partially attributed to outbreaks of infectious diseases, such as smallpox, measles and diphtheria, that were imported from Europe and to which the invaders were mostly immune. It is estimated that the population of Mexico was reduced to one-tenth of its previous size between 1519 and 1530 [9]. Further examples can be found in the book by McNeill [34], to which the reader interested in the history of epidemics is referred. In view of the importance of infectious diseases, people naturally started investigating their causes and searching for treatments; one of the oldest accounts is the book by Hippocrates [25] (see also [31]), who is often referred to as the father of Western medicine. The existence of microorganisms was not discovered before the seventeenth century, with the aid of the first microscopes; however, their role in the spread of infectious diseases was understood much later [22]: a first theory of infectious agents (also called pathogens) was developed only in the latter part of the nineteenth century [9].

The first application of mathematical modelling to infectious diseases is due to Bernoulli [5] (see also [6]), who developed models to understand the effectiveness of a mass vaccination campaign against smallpox in increasing life expectancy. The foundations of the mathematical epidemiology of infectious diseases were laid only about a century later by En'ko [17] (see also [15, 18]), Ross [38], and Kermack and McKendrick [27, 28, 29]; as we shall see, some of their ideas, such as that of a threshold behaviour, can still be found in more recent models.

The aim of mathematical epidemiology of infectious diseases is threefold [13, Ch. 1]: (a) the first objective is to understand the biological and social mechanisms of disease spread by means of an appropriate mathematical structure that models available data; (b) the second goal is prediction of future epidemics, including assessment of the possible impact of outbreaks and estimation of associated medical costs; (c) the third aim is to understand how the spread may be controlled, for example through education, immunization and isolation, by introducing these measures in the model

and assessing their effectiveness before the actual implementation. Depending on the disease, different management methods may be available: these include prevention (such as public information campaigns and vaccination), treatment of symptomatic patients (if a cure is known), and attempts at controlling by isolation of diagnosed patients and quarantine of suspected cases. However, these strategies are almost impossible to compare unless suitable mathematical models are available to describe the resulting scenarios, since epidemiological experiments with control groups are not only very difficult to plan, but also pose serious ethical questions due to withholding treatment from the control group [22]. Moreover, because of the long time scale on which some diseases run, such clinical trials would necessarily last many years [9].

Furthermore, as is common in mathematical modelling, there is always a trade-off between simple and detailed models: on one hand, simple models may be analytically solvable, but fail to capture even the essential properties of a disease; on the other hand, detailed models may be so difficult to solve that proper analysis of their behaviour is impossible. Moreover, detailed models usually require more parameters, whose estimation from available data, which is often sparse and inaccurate, is particularly troublesome.

In this context, a parameter of particular interest is the so-called infection rate, whose estimation is particularly difficult since it cannot be directly inferred through clinical observation. This thesis focuses on estimation of this crucial parameter in a particular class of epidemic models that consider multiple populations, and is organized as follows.

Chapter 2 and 3 are devoted to presenting the main definitions and results that will be used later in the text. In particular, Chapter 2 is concerned with stochastic processes, whereas Chapter 3 deals with graph theory. After this technical introduction we review, in Chapter 4, the common assumptions behind most epidemic models, and then proceed to introduce the classic deterministic and stochastic models proposed in the literature. In Chapter 5, we present two possible applications of graph theory to these models, namely: (a) population models, which consider disease spread at the level of individuals belonging to a single population; (b) meta-population models, which consider disease spread in a system with multiple populations. Focusing on meta-population models, in Chapter 6 we then introduce our estimation method for the infection rate starting only from knowledge of the arrival times of the first infective individual in each population. This method is then tested by means of a number of computer simulations. Finally, in Chapter 7, we present our conclusions and indicate possible directions for future work.

CHAPTER 2

Stochastic processes

2.1. Basic definitions

In what follows, we shall denote by $X(t)$ a random variable indexed by a quantity t that represents time. The possible values of this random variable constitute its state space \mathcal{S} , which may be either discrete, $\mathcal{S} = \{0, 1, \dots\}$, or continuous, $\mathcal{S} \subseteq \mathbb{R}$. At a fixed time t , the random variable $X(t)$ has an associated probability mass function or probability density function $p_t(x)$,

$$(2.1a) \quad \mathbb{P}[X(t) = x \in \mathcal{S}] = p_t(x) \quad (\text{discrete case}),$$

$$(2.1b) \quad \mathbb{P}[X(t) \in [a, b] \subseteq \mathcal{S}] = \int_a^b p_t(x) dx \quad (\text{continuous case}).$$

DEFINITION 2.1 (Stochastic process). A stochastic process is a family of random variables $\{X(t)\}$ indexed by the same quantity t , which is usually understood to represent time and which can be considered either discrete or continuous. In the case of a discrete time stochastic process, t will belong to a discrete set of (possibly equispaced) instants, whereas for a continuous time stochastic process it will belong to the open interval $[0, +\infty)$.

REMARK 2.1. To avoid a burdensome notation, when considering discrete time we shall write X_{t+1} to denote the random variable X at the instant immediately following t .

DEFINITION 2.2 (Markov property). A discrete time stochastic process is said to satisfy the Markov property if

$$(2.2) \quad \mathbb{P}[X_{t+1} | X_t, X_{t-1}, \dots] = \mathbb{P}[X_{t+1} | X_t],$$

i.e., when its future state depends at most on its current state. Similarly, a continuous time stochastic process is said to satisfy the Markov property if

$$(2.3) \quad \mathbb{P}[X(t_{n+1}) | X(t_0), X(t_1), \dots, X(t_n)] = \mathbb{P}[X(t_{n+1}) | X(t_n)]$$

for any ordered sequence of real numbers $0 \leq t_0 < t_1 < \dots < t_n < t_{n+1}$.

DEFINITION 2.3 (Markov chain). A Markov chain is a stochastic process that satisfies the Markov property and whose state space \mathcal{S} is countable. Intuitively, a Markov chain undergoes transitions among the countably many possible states in a chainlike manner (often described by a directed weighted graph, see Chapter 3); moreover, since it satisfies the Markov property, the next state depends only on the current state.

DEFINITION 2.4 (Infinitesimal generator matrix). A Markov chain with n states can also be characterized by a square matrix $\mathbf{Q} = (q_{ij})$ of order n , called the infinitesimal generator matrix, whose generic element q_{ij} , $i, j \in \mathcal{S}$, $i \neq j$, corresponds to the instantaneous transition rate from state i to state j , and diagonal elements are chosen so that rows sum to zero,

$$(2.4) \quad q_{ii} = - \sum_{j \neq i} q_{ij} \quad \text{for all } i \in \mathcal{S}.$$

DEFINITION 2.5 (Transient and recurrent state). Given a Markov chain $\{X(t), t \geq 0\}$ with state space \mathcal{S} , let us denote by R_s the random variable representing the first return time to state $s \in \mathcal{S}$ given that the chain started in that same state,

$$(2.5) \quad R_s = \inf_{t > 0} \{X(t) = s \mid X(0) = s\}.$$

A state $s \in \mathcal{S}$ is said to be transient if, starting in that state, there is a non-zero probability that the chain will never be in that state again in the future, $\mathbb{P}[R_s < \infty] < 1$; otherwise, it is said to be recurrent or persistent.

DEFINITION 2.6 (Absorbing state). Given a Markov chain with state space \mathcal{S} , a state $s \in \mathcal{S}$ is said to be absorbing if and only if it is impossible to leave it, i.e. if the probabilities of transitioning to any other different state are all zero.

DEFINITION 2.7 (Birth-death process). A birth-death process is a continuous time Markov chain whose states represent the size of a population and whose transitions are limited to unitary births, corresponding to transitions of type $k \rightarrow k + 1$, and unitary deaths, corresponding to transitions of type $k \rightarrow k - 1$. A birth-death process is fully specified by the birth rates $\{\lambda_i, i = 0, 1, \dots\}$ and the death rates $\{\mu_i, i = 1, 2, \dots\}$. Its state diagram is shown in Figure 2.1.

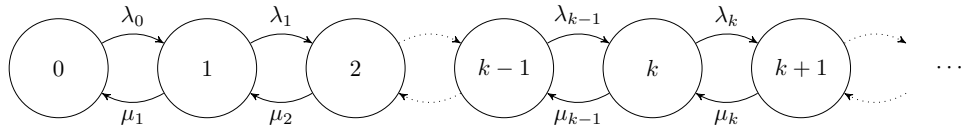


FIGURE 2.1. State diagram of a birth-death process.

DEFINITION 2.8 (Phase-type distribution). Denote by $\{X(t), t \geq 0\}$ an homogeneous Markov process with finite state space $\mathcal{S}_X = \{1, \dots, n+1\}$, where we assume that states $1, \dots, n$ are transient, while state $n+1$ is absorbing. Therefore, the infinitesimal generator matrix of $X(t)$ is of the following form,

$$(2.6) \quad \mathbf{Q} = \begin{pmatrix} \mathbf{T} & \boldsymbol{\eta} \\ \mathbf{0} & 0 \end{pmatrix},$$

where \mathbf{T} is a square matrix of order n , $\boldsymbol{\eta}$ is a column vector of dimension n called the exit vector, and $\mathbf{0}$ is the zero row vector of the same dimension. Denoting by $\mathbf{1}$ the column vector of dimension n whose entries are all equal to one, we have that $\boldsymbol{\eta} = -\mathbf{T} \mathbf{1}$. The initial distribution of $X(t)$ is given by the vector

$$(2.7) \quad \tilde{\boldsymbol{\alpha}} = (\boldsymbol{\alpha}, \alpha_{n+1}),$$

where $\boldsymbol{\alpha}$ is a row vector of dimension n and $\alpha_{n+1} = 1 - \boldsymbol{\alpha} \mathbf{1}$.

The random variable T^* , denoting the time until absorption in state $n + 1$, is said to be distributed according to a phase-type distribution of order n with parameters $\boldsymbol{\alpha}$ and \mathbf{T} , and we write $T^* \sim \text{PH}(\boldsymbol{\alpha}, \mathbf{T})$. It can be proven (see, for example, [10, Ch. 9]) that the cumulative distribution function of T^* is given by

$$(2.8) \quad F^*(t) = 1 - \boldsymbol{\alpha} e^{\mathbf{T}t} \mathbf{1}, \quad t \geq 0,$$

and that its probability density function is given by

$$(2.9) \quad f^*(t) = \boldsymbol{\alpha} e^{\mathbf{T}t} \boldsymbol{\eta}, \quad t \geq 0,$$

where $e^{\mathbf{T}t} = \sum_{k=0}^{\infty} \frac{t^k}{k!} \mathbf{T}^k$ denotes the matrix exponential. Moreover, its moments are as follows,

$$(2.10) \quad \mathbb{E}[(T^*)^n] = (-1)^n n! \boldsymbol{\alpha} \mathbf{T}^{-n} \mathbf{1}, \quad n \in \mathbb{N}.$$

2.2. Non-homogeneous Poisson processes

DEFINITION 2.9 (Counting process). A stochastic process $\{N(t), t \geq 0\}$ is said to be a counting process if the following conditions hold, for all $s, t \geq 0$,

- (1) $N(t) \in \mathbb{N}$,
- (2) $s \leq t \Rightarrow N(s) \leq N(t)$.

If $s < t$, then $N(t) - N(s)$ is the number of events that occurred during the interval $(s, t]$.

DEFINITION 2.10 (Non-homogeneous Poisson process). A counting process $\{N(t), t \geq 0\}$ is said to be a non-homogeneous Poisson process with time-dependent rate $\lambda(t) \geq 0, t \geq 0$, if the following conditions hold,

- (1) $N(0) = 0$,
- (2) $\{N(t), t \geq 0\}$ has independent increments,
- (3) $\mathbb{P}[N(t + \Delta_t) - N(t) = 1] = \lambda(t) \Delta_t + o(\Delta_t)$,
- (4) $\mathbb{P}[N(t + \Delta_t) - N(t) \geq 2] = o(\Delta_t)$,

where $o(\Delta_t)$ is such that

$$(2.11) \quad \lim_{\Delta_t \rightarrow 0} \frac{o(\Delta_t)}{\Delta_t} = 0.$$

DEFINITION 2.11 (Homogeneous Poisson process). A homogeneous Poisson process is a non-homogeneous Poisson process whose rate is constant, $\lambda(t) = \lambda$ for all $t \geq 0$.

THEOREM 2.1. *Let $\{N(t), t \geq 0\}$ be a non-homogeneous Poisson process with time-dependent rate $\lambda(t)$. We have that*

$$(2.12) \quad N(t + \Delta_t) - N(t) \sim \text{Poisson}(\Lambda(t + \Delta_t) - \Lambda(t))$$

where

$$(2.13) \quad \Lambda(t) = \int_0^t \lambda(\tau) d\tau.$$

PROOF. The proof of Theorem 2.1 can be found in classic books on stochastic processes, such as the ones by Ross [39, Ch. 2] and Lefebvre [30, Ch. 5], to which the interested reader is referred. \square

COROLLARY 2.1. *Let $\{N(t), t \geq 0\}$ be a non-homogeneous Poisson process with time-dependent rate $\lambda(t)$. It follows immediately from Theorem 2.1 that*

$$(2.14) \quad N(t) \sim \text{Poisson}(\Lambda(t)).$$

2.2.1. Distribution of the first arrival time. We now derive the main result that links the probability distribution of the time of the first arrival in a non-homogeneous Poisson process with time-dependent rate $\lambda(t)$ with this rate function itself. Moreover, we use this result to show the relation between particular forms of $\lambda(t)$ and well-known probability distributions for the time of the first arrival.

LEMMA 2.1. *Denote by T^* the random variable representing the time of the first arrival in a non-homogeneous Poisson process $\{N(t), t \geq 0\}$ with time-dependent rate $\lambda(t)$. The cumulative distribution function of T^* at time t , i.e. the probability that the first arrival occurs before or at time t , can be rewritten in terms of $\Lambda(t)$ as follows,*

$$(2.15) \quad F^*(t) = 1 - e^{-\Lambda(t)}.$$

Its probability density function is thus given by

$$(2.16) \quad f^*(t) = \frac{dF^*}{dt} = \lambda(t) e^{-\Lambda(t)}.$$

PROOF. The probability that the first arrival occurs before or at time t is equivalent to the probability that at least one arrival occurred during the interval $[0, t]$,

$$(2.17) \quad \begin{aligned} F^*(t) &= \mathbb{P}[N(t) \geq 1] \\ &= 1 - \mathbb{P}[N(t) = 0] \\ &= 1 - e^{-\Lambda(t)}. \end{aligned}$$

Differentiating the previous equation with respect to t yields

$$(2.18) \quad f^*(t) = \frac{dF^*}{dt} = \lambda(t) e^{-\Lambda(t)},$$

which is what we wanted to prove. \square

THEOREM 2.2. *Given a random variable T whose distribution is given by the cumulative distribution function $F(t)$, $t \in \mathbb{R}$, denote the associated probability density function by $f(t)$, $t \in \mathbb{R}$, and define the conditioned random variable $T^* = T | T \geq 0$. Note that T coincides with T^* if and only if the support of its distribution is limited to the interval $[0, +\infty)$. The probability density function of T^* is given by*

$$(2.19) \quad f^*(t) = \frac{f(t)}{1 - F(0)}, \quad t \geq 0,$$

and its cumulative distribution function by

$$(2.20) \quad F^*(t) = \int_0^t f^*(\tau) d\tau = \frac{F(t) - F(0)}{1 - F(0)}, \quad t \geq 0.$$

The random variable T^* represents the time of the first arrival in a non-homogeneous Poisson process with time-dependent rate $\lambda(t)$ if and only if

$$(2.21) \quad \lambda(t) = \frac{f^*(t)}{1 - F^*(t)} = \frac{f(t)}{1 - F(t)}, \quad t \geq 0.$$

PROOF. By Lemma 2.1, we know that the cumulative distribution function of the random variable T^* is given by

$$(2.22) \quad F^*(t) = 1 - e^{-\Lambda(t)}.$$

Simple algebraic manipulation immediately yields Equation (2.21), which is what we wanted to prove. \square

COROLLARY 2.2. *The time T^* of the first arrival in a homogeneous Poisson process with fixed rate λ is distributed according to an exponential distribution with parameter λ .*

PROOF. This is a special case in which

$$(2.23) \quad \lambda(t) = \lambda, \quad t \geq 0.$$

By Theorem 2.2, we only have to prove that

$$(2.24) \quad \frac{f(t)}{1 - F(t)} = \lambda,$$

where $f(t)$ and $F(t)$ are the probability density function and the cumulative distribution function, respectively, of an exponential distribution with parameter λ . In fact, we have that

$$(2.25) \quad f(t) = \lambda e^{-\lambda t} \quad \text{and} \quad F(t) = 1 - e^{-\lambda t},$$

from which Equation (2.24) immediately follows. \square

DEFINITION 2.12 (Weibull distribution). A random variable X is said to be distributed according to a Weibull distribution with shape parameter $k \in \mathbb{R}$, $k > 0$, and scale parameter $\lambda \in \mathbb{R}$, $\lambda > 0$, and we write $X \sim \Psi(k, \lambda)$, if it has probability density function

$$(2.26) \quad f_X(x) = \frac{k}{\lambda} \left(\frac{x}{\lambda} \right)^{k-1} e^{-(x/\lambda)^k}, \quad x \geq 0,$$

and cumulative distribution function

$$(2.27) \quad F_X(x) = \int_0^x f_X(t) dt = 1 - e^{-(x/\lambda)^k}, \quad x \geq 0.$$

Its first moment is given by

$$(2.28) \quad \mathbb{E}[X] = \lambda \Gamma\left(1 + \frac{1}{k}\right),$$

where $\Gamma(z)$ is the Gamma function.

COROLLARY 2.3. *The time T^* of the first arrival in a non-homogeneous Poisson process is distributed according to a Weibull distribution with parameters*

$$(2.29) \quad k = \beta \quad \text{and} \quad \lambda = \left(\frac{\beta}{\alpha}\right)^{1/\beta}$$

if and only if the time-dependent rate $\lambda(t)$ is of the form

$$(2.30) \quad \lambda(t) = \alpha t^{\beta-1}, \quad t \geq 0, \quad \alpha, \beta > 0.$$

PROOF. By Theorem 2.2, we only have to prove that

$$(2.31) \quad \frac{f(t)}{1 - F(t)} = \alpha t^{\beta-1},$$

where $f(t)$ and $F(t)$ are the probability density function and the cumulative distribution function, respectively, of a Weibull distribution with parameters as per Equation (2.29). In fact, we have that

$$(2.32) \quad f(t) = \alpha t^{\beta-1} e^{-\alpha t^{\beta}/\beta} \quad \text{and} \quad F(t) = 1 - e^{-\alpha t^{\beta}/\beta},$$

from which Equation (2.31) immediately follows. \square

DEFINITION 2.13 (Gumbel distribution). A random variable X is said to be distributed according to a Gumbel distribution with location parameter $\mu \in \mathbb{R}$ and scale parameter $\sigma \in \mathbb{R}$, $\sigma > 0$, and we write $X \sim \Lambda(\mu, \sigma)$, if it has probability density function

$$(2.33) \quad f_X(x) = \frac{z e^{-z}}{\sigma}, \quad z = e^{(x-\mu)/\sigma}, \quad x \in \mathbb{R},$$

and cumulative distribution function

$$(2.34) \quad F_X(x) = \int_{-\infty}^x f_X(t) dt = 1 - e^{-z}, \quad x \in \mathbb{R}.$$

Its first moment is given by

$$(2.35) \quad \mathbb{E}[X] = \mu - \gamma\sigma,$$

where $\gamma \approx 0.57722$ is the Euler-Mascheroni constant.

DEFINITION 2.14 (Non-negative Gumbel distribution). Given a random variable $X \sim \Lambda(\mu, \sigma)$, let us define the conditioned random variable $X^+ = X | X \geq 0$. The random variable X^+ is said to be distributed according

to a non-negative Gumbel distribution, and we write $X \sim \Lambda^+(\mu, \sigma)$; it has probability density function

$$(2.36) \quad f_X^+(x) = \frac{f_X(x)}{\mathbb{P}[X \geq 0]} = \frac{f_X(x)}{1 - F_X(0)} = \frac{z}{\sigma} e^{-z+e^{-\mu/\sigma}}, \quad z = e^{(x-\mu)/\sigma}, \quad x \geq 0,$$

and cumulative distribution function

$$(2.37) \quad F_X^+(x) = \int_0^x f_X^+(t) dt = 1 - e^{-z+e^{-\mu/\sigma}}, \quad z = e^{(x-\mu)/\sigma}, \quad x \geq 0.$$

Its first moment is given by

$$(2.38) \quad \mathbb{E}[X^+] = \sigma e^{e^{-\mu/\sigma}} \Gamma\left(0, e^{-\frac{\mu}{\sigma}}\right),$$

where $\Gamma(a, z)$ is the incomplete Gamma function.

COROLLARY 2.4. *The time T^* of the first arrival in a non-homogeneous Poisson process is distributed according to a non-negative Gumbel distribution with parameters*

$$(2.39) \quad \mu = -\frac{1}{\beta} \ln \frac{\alpha}{\beta} \quad \text{and} \quad \sigma = \frac{1}{\beta}$$

if and only if the time-dependent rate $\lambda(t)$ is of the form

$$(2.40) \quad \lambda(t) = \alpha e^{\beta t}, \quad t \geq 0, \quad \alpha, \beta > 0.$$

PROOF. By Theorem 2.2, we only have to prove that

$$(2.41) \quad \frac{f(t)}{1 - F(t)} = \alpha e^{\beta t},$$

where $f(t)$ and $F(t)$ are the probability density function and the cumulative distribution function, respectively, of a standard Gumbel distribution with parameters as per Equation (2.39). In fact, we have that

$$(2.42) \quad f(t) = \alpha e^{-\alpha e^{\beta t}/\beta + \beta t} \quad \text{and} \quad F(t) = 1 - e^{-\alpha e^{\beta t}/\beta},$$

from which Equation (2.41) immediately follows. \square

CHAPTER 3

Basic concepts from graph theory

In this short presentation we shall only introduce some standard concepts from graph theory, without any pretension of providing a complete account of this vast field of research, for which we refer the interested reader to introductory books such as the one by Diestel [14].

Generally speaking, graphs are composed of a finite set of vertices \mathcal{V} that represent elements of the system being modelled, and a binary relation $E \subseteq \mathcal{V}^2$ that represents edges, i.e. pairwise interactions between the vertices. While it is possible to consider edges that link a vertex $i \in \mathcal{V}$ to itself, called self-loops, in what follows we shall only be concerned with graphs without self-loops; more formally, this is equivalent to requiring that the binary relation E is irreflexive, $(i, i) \notin E$ for all $i \in \mathcal{V}$.

3.1. Graphs

The simplest kind of graph that we shall consider are those in which relations between elements of the system are symmetric. An example is shown in Figure 3.1.

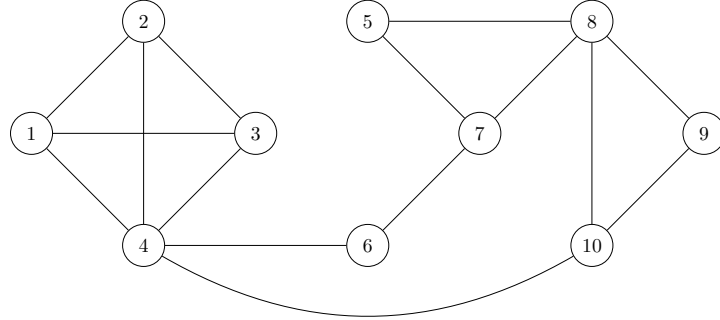


FIGURE 3.1. Example of graph with $n = 10$ vertices and $m = 15$ edges.

DEFINITION 3.1 (Graph). A graph is a couple (\mathcal{V}, E) , where $\mathcal{V} = \{1, 2, \dots, n\}$ is a finite set of vertices (or nodes), and $E \subseteq \mathcal{V}^2$ is a binary relation over it describing the edges and satisfying, for all $i, j \in \mathcal{V}$,

$$(3.1a) \quad (i, i) \notin E \quad \text{(irreflexivity)}$$

$$(3.1b) \quad (i, j) \in E \Rightarrow (j, i) \in E \quad \text{(symmetry)}$$

Because of symmetry, it is common to define an edge as the pair $\{(i, j), (j, i)\}$.

We shall now introduce some useful terminology regarding basic characteristics of a graph, such as the number of vertices or edges it contains.

DEFINITION 3.2 (Adjacent vertices or neighbours). Two vertices $i, j \in \mathcal{V}$ linked by an edge, $(i, j) \in E$, are said to be adjacent or neighbours.

For example, vertices 1 and 2 in Figure 3.1 are adjacent or neighbours.

DEFINITION 3.3 (Order of a graph). The order of a graph, commonly denoted n , is the number of its vertices, i.e. the cardinality of the set \mathcal{V} .

For example, the graph of Figure 3.1 is of order 10.

DEFINITION 3.4 (Size of a graph). The size of a graph, commonly denoted m , is the number of its edges. Since edges are commonly defined as the pairs $\{(i, j), (j, i)\}$, this number corresponds to half the cardinality of the binary relation E .

For example, the graph of Figure 3.1 is of size 15.

REMARK 3.1 (Maximum size). The size m of a graph is clearly connected to its order n . Because of the irreflexivity requirement, the maximum cardinality of E is $n(n-1)$; this situation corresponds to the complete graph, in which each vertex is connected to all others. Therefore, the maximum size of a graph of order n is $m_{\max} = n(n-1)/2$.

DEFINITION 3.5 (Adjacency matrix). The binary relation E can be explicitly represented by a square symmetric matrix $\mathbf{A} = \mathbf{A}^T$ of order n , called adjacency matrix, with elements

$$(3.2) \quad a_{ij} = \begin{cases} 1 & \text{if } (i, j) \in E \\ 0 & \text{otherwise} \end{cases} \quad \text{for all } i, j \in \mathcal{V}.$$

DEFINITION 3.6 (Vertex degree). The degree k_i of a vertex $i \in \mathcal{V}$ is defined as the number of its neighbours. From the point of view of the binary relation E , this corresponds to the cardinality of the subset of E containing only tuples whose first element is i , or equivalently to the cardinality of the subset of E containing only tuples whose second element is i . In terms of the adjacency matrix \mathbf{A} we have that

$$(3.3) \quad k_i = \sum_{j \neq i} a_{ij} = \sum_{j \neq i} a_{ji}.$$

For example, vertex 1 in Figure 3.1 has degree 3.

DEFINITION 3.7 (Degree distribution). Given a graph, let p_k be the fraction of its vertices that have degree k . The sequence $\{p_k : k = 0, \dots, n-1\}$ is called degree distribution and represents the probability of a randomly chosen vertex having degree k .

For example, the degree distribution of the graph shown in Figure 3.1 is $\{0, 0, 0.3, 0.5, 0.1, 0.1, 0, 0, 0\}$, since it has no vertex with degree zero or one, three vertices with degree two, five vertices with degree three, one vertex with degree four, one vertex with degree five, and no other vertex with higher degree.

REMARK 3.2. Naturally, the degree distribution does not fully determine the structure of the graph. Typically, there is a significant number of graphs sharing the same degree distribution.

3.1.1. Weighted graphs. A simple extension of graphs consists in associating to each edge a non-negative weight that is usually assumed to represent the strength of the relation; an alternative definition requires that weights belong to the $[0, 1]$ interval, an assumption which can always be satisfied by an appropriate rescaling of the values.

It is particularly easy to think of weighted graphs in terms of their adjacency matrix representation. In this case, instead of the boolean matrices of simple graphs, we consider adjacency matrices whose elements can take any non-negative real value,

$$(3.4) \quad a_{ij} = a_{ji} \geq 0 \quad \text{for all } i, j \in \mathcal{V}, i \neq j.$$

DEFINITION 3.8 (Adjacent vertices or neighbours). Two vertices $i, j \in \mathcal{V}$ are said to be adjacent or neighbours if $a_{ij} > 0$.

DEFINITION 3.9 (Vertex degree). The degree k_i of a vertex $i \in \mathcal{V}$ is again defined as the number of its neighbours,

$$(3.5) \quad k_i = \sum_{j \neq i} H(a_{ij}) = \sum_{j \neq i} H(a_{ji}),$$

where $H(x)$ is the Heaviside step function whose value is one for $x > 0$ and zero otherwise.

DEFINITION 3.10 (Vertex strength). The strength s_i of a vertex $i \in \mathcal{V}$ is defined as the sum of the weights of all edges that link it to other vertices,

$$(3.6) \quad s_i = \sum_{j \neq i} a_{ij} = \sum_{j \neq i} a_{ji}.$$

Note that, in general, the degree k_i of a vertex $i \in \mathcal{V}$ is not the same as its strength s_i .

3.2. Digraphs

DEFINITION 3.11 (Digraph). Digraphs (from “directed graphs”) are obtained by relaxing the symmetry requirement of Definition 3.1, thus allowing each edge to have a direction, commonly represented by an arrow as in Figure 3.2. In this case, the adjacency matrix \mathbf{A} is also asymmetric.

DEFINITION 3.12 (Adjacent vertices or neighbours). Two vertices $i, j \in \mathcal{V}$ are said to be adjacent or neighbours if $(i, j) \in E$ or $(j, i) \in E$.

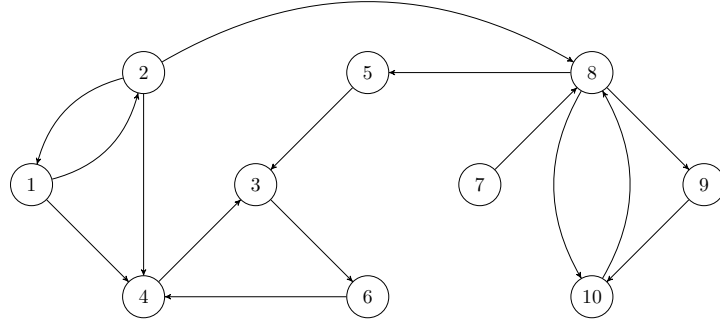


FIGURE 3.2. Example of digraph with $n = 10$ vertices and $m = 15$ edges.

For example, vertices 1 and 2 in Figure 3.2 are adjacent or neighbours, and so are 1 and 4. Definition 3.3 also applies to the order of a digraph; its size, however, needs to be redefined as follows.

DEFINITION 3.13 (Size of a digraph). The size of a digraph, commonly denoted m , is the number of its edges, which corresponds to the cardinality of the binary relation E .

REMARK 3.3 (Maximum size). Because of the irreflexivity requirement, the maximum cardinality of E is $n(n - 1)$; therefore, the maximum size of a digraph of order n is $m_{\max} = n(n - 1)$.

Moreover, in digraphs it is not possible to define the degree as we did in Definition 3.6, because the number of edges pointing to a vertex $i \in \mathcal{V}$ is generally different from the number of edges pointing from i to other vertices.

DEFINITION 3.14 (Vertex in-degree and out-degree). The in-degree k_i^{in} of a vertex $i \in \mathcal{V}$ is defined as the number of incoming edges, i.e. edges that start at one of the neighbours of i and end at i ; in terms of the binary relation E , this corresponds to the cardinality of the subset of E containing only tuples whose second element is i . Similarly, the *out-degree* k_i^{out} of the same vertex i is defined as the number of outgoing edges, i.e. edges that start at i and end at one of its neighbours; in terms of the binary relation E , this corresponds to the cardinality of the subset of E containing only tuples whose first element is i . As regards the adjacency matrix \mathbf{A} , we have that

$$(3.7) \quad k_i^{\text{in}} = \sum_j a_{ji} \quad \text{and} \quad k_i^{\text{out}} = \sum_j a_{ij}.$$

For example, the in-degree of vertex 1 in Figure 3.2 is 1, while its out-degree is 2. It is also possible, but not common, to define the distributions of the in-degrees and out-degrees.

3.2.1. Weighted digraphs. As for graphs, digraphs can also be extended to include non-negative weights associated to each edge. In this case, the adjacency matrix \mathbf{A} is not only asymmetric, but its elements a_{ij} can take any non-negative real value, $a_{ij} \geq 0$ for all $i, j \in \mathcal{V}$, $i \neq j$.

DEFINITION 3.15 (Adjacent vertices or neighbours). Two vertices $i, j \in \mathcal{V}$ are said to be adjacent or neighbours if $a_{ij} > 0$ or $a_{ji} > 0$.

DEFINITION 3.16 (Vertex in-degree and out-degree). The in-degree k_i^{in} and the out-degree k_i^{out} of a vertex $i \in \mathcal{V}$ are again defined as the number of incoming and outgoing edges, respectively,

$$(3.8) \quad k_i^{\text{in}} = \sum_j H(a_{ji}) \quad \text{and} \quad k_i^{\text{out}} = \sum_j H(a_{ij}),$$

where $H(x)$ is the Heaviside step function whose value is one for $x > 0$ and zero otherwise.

It is also possible, but not common, to define the in-strength and out-strength by generalization of Definition 3.10.

CHAPTER 4

Mathematical epidemiology of infectious diseases

4.1. Modelling assumptions

Many mathematical models for the spread of infectious diseases have been proposed in the literature, and it is often too easy to get lost in their details. Since models necessarily encompass a set of assumptions, it makes sense to classify them according to the hypotheses they are based on [13, Ch. 1]. As shown in Figure 4.1, assumptions roughly belong to three main categories, namely:

- (1) assumptions about the disease itself;
- (2) assumptions about the environment within which the disease spreads;
- (3) assumptions due to mathematical modelling.

Assumptions about the disease mostly regard the possible states (also sometimes called compartments) according to which individuals are exclusively and exhaustively classified at any given time, and dynamics among them. In this work we shall restrict ourselves to contagious illnesses, under the basic assumption that diseases spread as a result of contacts between susceptible and infective (carrier) individuals¹. In this context, models range from the simplest $S \rightarrow I$ model, in which individuals are either susceptible to the disease (S) or forever infected with it (I), to more complex extensions that account for different stages of infection (such as incubation periods), temporary recovery, removals (which may themselves be due to different causes, such as acquired immunity, isolation, or death), vaccinations and vertical transmission and immunity. Of course, realistic assumptions about the disease can only be formulated based on the epidemiological properties of the pathogen. However, the time scale being considered also plays a crucial role: in the case of influenza, for example, it is reasonable and often easier to assume that, in a single season, an individual can only catch the disease once, and thus earns “lifelong” immunity after the infection.

Assumptions regarding the environment can be further classified into two subcategories: assumptions about its structure and about its dynamics. As for structure, an important distinction needs to be made between population models, which deal with a single population, and meta-population

¹Note that this assumption does indeed exclude a number of diseases, for example those that spread through intermediate vector species (such as mosquito for malaria and yellow fever). It is of course possible to model these illnesses as well, and one of the landmarks in the development of mathematical epidemiology is indeed the work of Ross [38] on malaria.

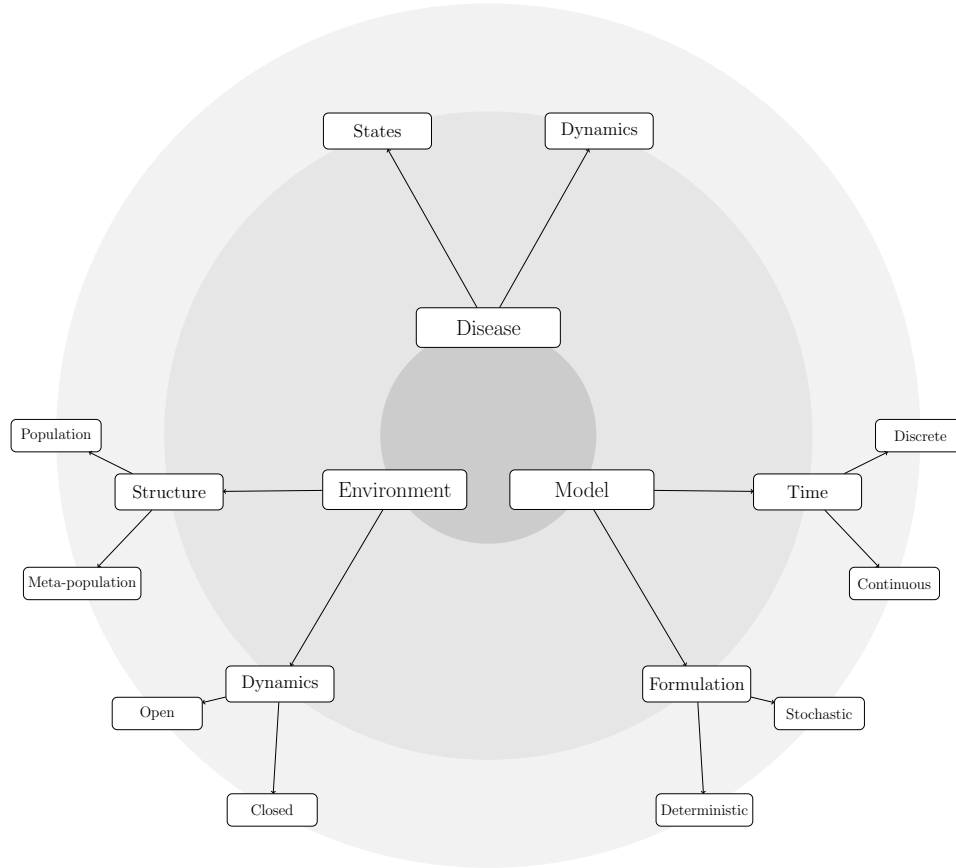


FIGURE 4.1. Categorization of assumptions in epidemiological models of infectious diseases: the three main categories include assumptions about the disease itself, the environment within which it spreads, and the mathematical model itself.

models, which consider a set of populations and constrained interactions among them, such as travel of individuals. The population (or populations, in the case of meta-population models) may be considered as a single, homogeneous group, as a collection of several homogeneous strata, or else as completely heterogeneous. In all cases it is also necessary to define the population dynamics, which range from closed populations, with a constant number of individuals, to open populations considering complex birth and death processes, as well as migrations.

Finally, assumptions due to mathematical modelling are usually needed in order to obtain analytical results. First of all, the formulation of a model can be either deterministic or stochastic, an important distinction which will be made clearer in the next paragraphs. Another major difference concerns whether time is considered as a discrete or continuous quantity. Since all data about epidemics is necessarily gathered at discrete time intervals, it often makes sense to assume that time is also discrete; however, since these

intervals can be made as small as desired, continuous time models can be considered as limiting cases, and usually offer interesting insights as well as better analytical tractability.

As said, the choice between deterministic and stochastic models is far more important than the one between discrete or continuous time, which can be made to correspond in the case of infinitesimal time increments. Historically, it is interesting to note that the development of deterministic and stochastic models has occurred almost in parallel. However, it is crucial to understand that the spread of infectious diseases is intrinsically a stochastic process: the same initial conditions may lead to very different outcomes, from small outbreaks to large-scale epidemics. It follows that any deterministic model that evolves according to fixed rules, depending only on initial parameter values, is at best an approximation of the actual process.

The effects of stochasticity are particularly relevant in the case of small populations [13, Ch. 3]. Even for larger populations, at the beginning of most outbreaks the number of infective individuals is usually small, so that the population might not mix homogeneously, making transmission of the disease depend strongly on the pattern of contacts [8].

As for the actual mathematical tools used, stochastic models are usually formulated as stochastic processes over a set of random variables representing the number of individuals in each state; their solutions are thus probability distributions for each random variable. On the other hand, deterministic models are often formulated as systems of differential or difference equations; their solutions are functions of discrete or continuous time that indicate the fraction of population in each state.

4.2. Deterministic models

4.2.1. The $S \rightarrow I$ model. The simplest epidemic model, due to Ross [38], contemplates only two states, the susceptible (S) and infective (I), and assumes that the disease spreads in a single closed population and that individuals mix homogeneously, so that each one has equal chance of becoming infective. Because of this last assumption, we can apply the law of mass action² and thus consider that the rate of interaction between the two sets of susceptible and infective individuals is proportional to the product of their cardinalities.

Let us denote by $S(t)$ and $I(t)$ the number of susceptible and infective individuals at time t , respectively, and by $s(t)$ and $i(t)$ the corresponding fractions of the population,

$$(4.1) \quad s(t) = \frac{S(t)}{N} \quad \text{and} \quad i(t) = \frac{I(t)}{N},$$

since the population size is assumed constant and equal to N . Taking into account the law of mass action, the $S \rightarrow I$ model can be schematized as

²This chemical law, due to Waage and Guldberg [42], states that, in a homogenous system, the rate of reaction is proportional to the active masses of reacting substances.

follows,

$$(4.2) \quad S \xrightarrow{\beta} I,$$

and formulated as the following system of non-linear ordinary differential equations,

$$(4.3a) \quad \frac{dS}{dt} = -\beta S(t) I(t),$$

$$(4.3b) \quad \frac{dI}{dt} = \beta S(t) I(t),$$

together with suitable initial conditions for the number of susceptible and infective individuals at time $t = 0$,

$$(4.4a) \quad S(0) = (1 - \alpha) N,$$

$$(4.4b) \quad I(0) = \alpha N,$$

where $0 \leq \alpha \leq 1$ is the fraction of population that is initially infective, $\beta > 0$ represents the per capita transmission rate, and clearly $S(0) + I(0) = N$ as required.

Since the population size is assumed constant, we have that $S(t) = N - I(t)$ at all time $t > 0$, which in turn means that the previous system has only one degree of freedom, and can be equivalently expressed by a single differential equation,

$$(4.5) \quad \frac{dI}{dt} = \beta I(t) (N - I(t)).$$

This equation can be explicitly solved by separation of variables, yielding

$$(4.6) \quad I(t) = \frac{I(0) N}{I(0) + (N - I(0)) e^{-\beta N t}},$$

from which it can be easily seen that, eventually, all individuals become infective,

$$(4.7) \quad \lim_{t \rightarrow +\infty} I(t) = \frac{I(0) N}{I(0)} = N.$$

Assuming that $I(0) = \alpha N$, $0 \leq \alpha \leq 1$ as per Equation (4.4b) and substituting in the equation above gives

$$(4.8) \quad I(t) = \frac{\alpha N}{\alpha + (1 - \alpha) e^{-\beta N t}}.$$

Figure 4.2 shows the evolution over time of the normalized quantity $i(t)$ for different values of β .

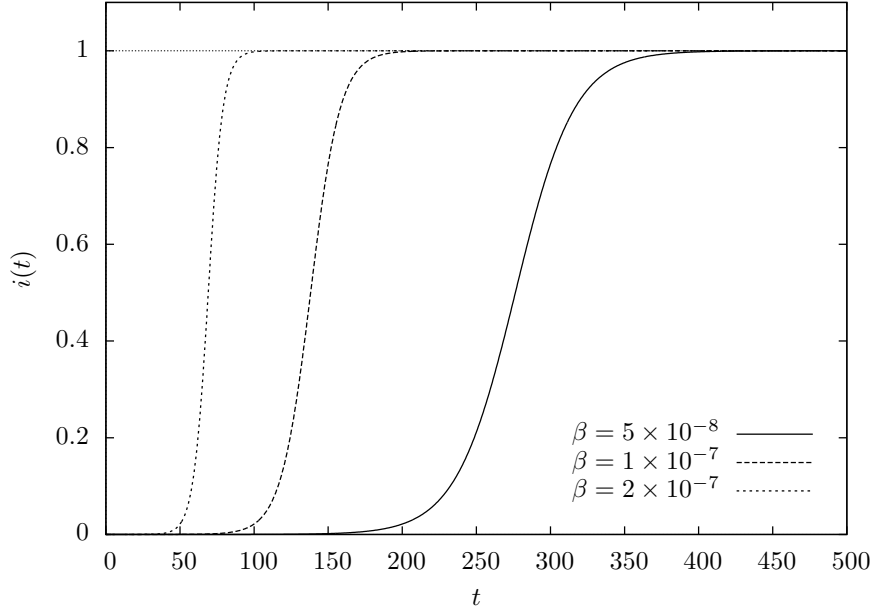


FIGURE 4.2. Evolution of the infective fraction of population in the deterministic $S \rightarrow I$ model for different values of β ; the population is of size $N = 10^6$ and initially a single individual is infective ($\alpha = N^{-1}$).

4.2.1.1. *Epidemic curve.* Another interesting function that can be immediately derived from Equation (4.8) is the epidemic curve $\dot{I}(t)$ that represents the rate of change of $I(t)$. This function is of particular interest since real-world data is usually made available in this form, i.e. as the number of new infective individuals over time. This means that model parameters could in principle be inferred by adjusting an epidemic curve to available data; however, the sparseness and inaccuracy that characterizes this information makes it very difficult to do so, which is why we consider a different approach in Chapter 6.

Differentiating Equation (4.8) yields

$$(4.9) \quad \dot{I}(t) = \frac{dI}{dt} = \frac{\alpha(1-\alpha)\beta N^2 e^{\beta N t}}{(\alpha(e^{\beta N t} - 1) + 1)^2},$$

some graphs of which are shown in Figure 4.3. This function is symmetric and unimodal; its maximum can be determined as the solution to the following equation,

$$(4.10) \quad \frac{d\dot{I}}{dt} = \frac{\alpha(\alpha-1)\beta^2 N^3 e^{\beta N t} (\alpha + \alpha e^{\beta N t} - 1)}{(\alpha(e^{\beta N t} - 1) + 1)^3} = 0,$$

which gives

$$(4.11) \quad t_{\max} = \frac{1}{\beta N} \ln \frac{1-\alpha}{\alpha} \quad \text{and} \quad \dot{I}(t_{\max}) = \frac{\beta N^2}{4}.$$

Furthermore, since

$$(4.12) \quad \lim_{N \rightarrow +\infty} t_{\max} = 0,$$

we note that, the larger the population, the sooner $\dot{I}(t)$ attains its maximum, as we would expect.

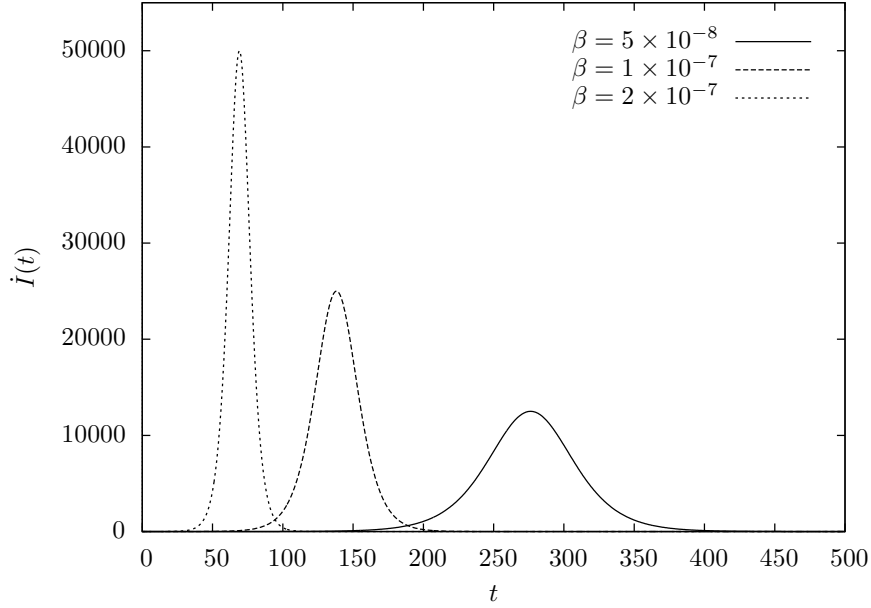


FIGURE 4.3. Epidemic curve in the deterministic $S \rightarrow I$ model for different values of β ; the population is of size $N = 10^6$ and initially a single individual is infective ($\alpha = N^{-1}$).

4.2.2. The $S \rightarrow I \rightarrow R$ model. A more complex epidemic model, due to Kermack and McKendrick [27, 28, 29], builds on the simpler $S \rightarrow I$ introduced in the previous section by considering a third state, the removed (R), which encompasses all infective individuals that no longer contribute to the spreading process and that cannot be reinfected. The rate of removal is assumed to be proportional to the number of infective individuals.

Given the above assumption, the $S \rightarrow I \rightarrow R$ model can be easily schematized as follows,

$$(4.13) \quad S \xrightarrow{\beta} I \xrightarrow{\gamma} R,$$

and formulated as the following system of non-linear ordinary differential equations,

$$(4.14a) \quad \frac{dS}{dt} = -\beta S(t) I(t),$$

$$(4.14b) \quad \frac{dI}{dt} = \beta S(t) I(t) - \gamma I(t),$$

$$(4.14c) \quad \frac{dR}{dt} = \gamma I(t),$$

where the parameter γ represents the instantaneous recovery rate, so that its reciprocal γ^{-1} represents the expected duration of the infectious period. In addition to specifying suitable initial conditions for the number of susceptible and infective individuals at time $t = 0$, one also needs to do so for the number of removed individuals $R(0)$ that, when greater than zero, can be interpreted as that part of the population that is initially immune to the disease. Similarly to the $S \rightarrow I$ model, since the population size is assumed constant, the previous system has only two degrees of freedom, and can be equivalently expressed by any two of the three differential equations together with the condition $S(t) + I(t) + R(t) = N$ at all time $t > 0$.

Despite being straightforward to formulate, the $S \rightarrow I \rightarrow R$ model cannot be solved analytically; as we shall see, however, a number of interesting properties can nonetheless be derived from analytical considerations.

4.2.2.1. The basic reproduction number R_0 . Suppose that all individuals in a population are initially susceptible, and that one of them becomes infective. This individual can be expected to infect the $S(0)$ susceptible individuals at a rate β during the expected infectious period γ^{-1} ; therefore, the total expected number of secondary cases it causes is given by

$$(4.15) \quad R_0 = \frac{\beta S(0)}{\gamma} \approx \frac{\beta N}{\gamma},$$

which is commonly known as the *basic reproduction number*. The number R_0 is of paramount importance in epidemic modelling: in particular, it determines whether an epidemic can occur at all³. Intuitively, since R_0 represents the expected number of secondary cases caused by introduction of a single infective individual into a completely susceptible population, no epidemic can develop if this number is smaller than one, since in this case the number of infective individuals in each successive generation decreases with time.

THEOREM 4.1 (Kermack-McKendrick Threshold Theorem). *A major outbreak occurs if and only if the rate of change at $t = 0$ of the number of infective individuals $I(0)$ is strictly positive; this happens if and only if $R_0 > 1$.*

PROOF. From Equation (4.14b), we have that the rate of change of the number of infective individuals $I(t)$ is strictly positive if and only if

$$(4.16) \quad \beta S(t) I(t) - \gamma I(t) > 0 \quad \text{or} \quad S(t) > \frac{\gamma}{\beta}.$$

Therefore, $I(t)$ increases as long as $S(t) > \gamma/\beta$; however, since $S(t)$ is a decreasing function of t , $I(t)$ must also ultimately decrease and approach zero. More specifically, if $S(0) < \gamma/\beta$, which corresponds to the condition

³The threshold behaviour that the $S \rightarrow I \rightarrow R$ model exhibits is not only consistent with observations, but has also become a broad principle in epidemiology of infectious diseases, having been rediscovered in a different form in many other models [9].

$R_0 < 1$, it does so immediately, and no epidemic takes place; otherwise, the so-called *epidemic regime* occurs: the function $I(t)$ first attains a maximum, when $S(t) = \gamma/\beta$, and then decreases to zero. \square

Figure 4.4 shows the evolution over time of the fractions of population in each of the three states in this second case.

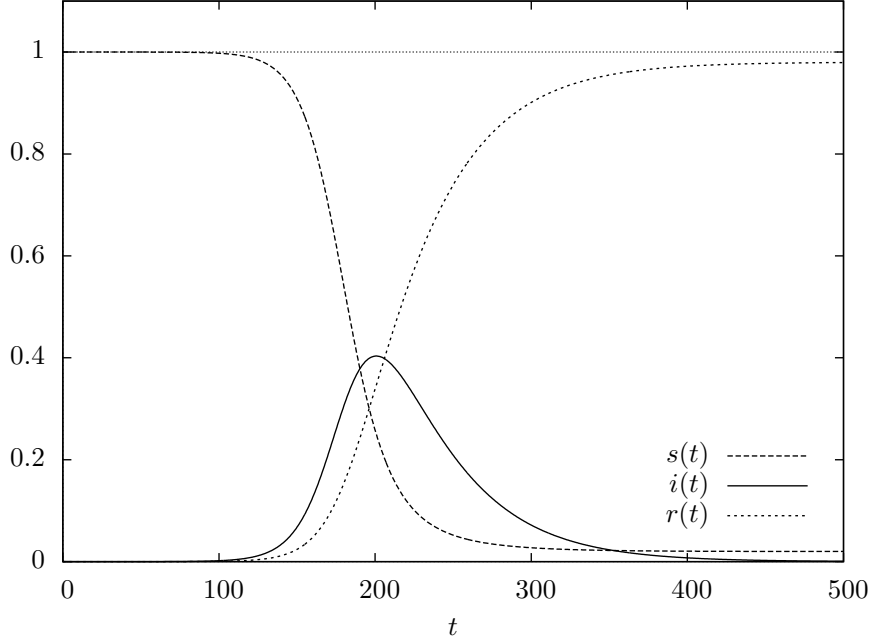


FIGURE 4.4. Evolution of the fractions of population in the three different states in the epidemic regime of the deterministic $S \rightarrow I \rightarrow R$ model with $\beta = 10^{-7}$, $\gamma = 0.025$, and a population of size $N = 10^6$, thus yielding $R_0 = 4$; initially a single individual is infective ($\alpha = N^{-1}$), while all others are susceptible.

4.2.2.2. Epidemic curve. As for the $S \rightarrow I$ model, it is possible to derive an expression for the epidemic curve associated with the $S \rightarrow I \rightarrow R$ model. However, instead of defining it as the rate of change of the number of infective individuals $I(t)$, as we did in Section 4.2.1.1, we shall consider the rate of change of the number of removed individuals $R(t)$. This definition is realistic if we assume that infective individuals are immediately removed when symptoms are detected, for example because they are quarantined or isolated to undergo treatment.

Dividing Equation (4.14a) by Equation (4.14c), we get the differential equation

$$(4.17) \quad \frac{dS}{dR} = \frac{-\beta S(t) I(t)}{\gamma I(t)} = -\frac{\beta}{\gamma} S(t)$$

that can be easily integrated (assuming $R(0) = 0$), yielding

$$(4.18) \quad S(t) = S(0) e^{-\beta R(t)/\gamma},$$

which, substituted into Equation (4.14c), gives

$$(4.19) \quad \frac{dR}{dt} = \gamma I(t) = \gamma (N - S(t) - R(t)) = \gamma \left(N - S(0) e^{-\frac{\beta}{\gamma} R(t)} - R(t) \right).$$

Considering now the quadratic Taylor polynomial approximation for the exponential term,

$$(4.20) \quad e^{-\frac{\beta}{\gamma} R(t)} \approx 1 - \frac{\beta}{\gamma} R(t) + \frac{\beta^2}{2\gamma^2} R^2(t),$$

we obtain the following approximation for Equation (4.14c),

$$(4.21) \quad \begin{aligned} \frac{dR}{dt} &\approx \gamma \left[N - S(0) \left(1 - \frac{\beta}{\gamma} R(t) + \frac{\beta^2}{2\gamma^2} R^2(t) \right) - R(t) \right] \\ &= \gamma \left[\frac{\beta^2 S(0)}{2\gamma^2} R^2(t) + \left(\frac{\beta S(0)}{\gamma} - 1 \right) R(t) + N - S(0) \right] \\ &= \gamma \left[\frac{R_0^2}{2S(0)} R^2(t) + (R_0 - 1) R(t) + N - S(0) \right], \end{aligned}$$

which can be explicitly solved by separation of variables (again assuming $R(0) = 0$), giving

$$(4.22) \quad R(t) \approx \frac{\gamma}{\beta R_0} \left[R_0 - 1 + \phi \tanh \left(\frac{\gamma \phi}{2} t - \psi \right) \right],$$

where we have defined

$$(4.23a) \quad \phi = \sqrt{(R_0 - 1)^2 - \frac{2\beta^2}{\gamma^2} S(0) I(0)},$$

$$(4.23b) \quad \psi = \operatorname{arctanh} \left(\frac{R_0 - 1}{\phi} \right).$$

By differentiation of Equation (4.22), we can obtain an approximate expression for the epidemic curve,

$$(4.24) \quad \dot{R}(t) \approx \frac{\gamma^3 \phi^2}{2\beta^2 S(0)} \operatorname{sech}^2 \left(\frac{\gamma \phi}{2} t - \psi \right),$$

some graphs of which are shown in Figure 4.5.

4.2.2.3. Final size of the epidemic. Another interesting consideration that can be made on purely analytical grounds regards the final size of the epidemic. It has been observed that many epidemics spread into a population and then disappear without infecting the entire population; intuitively, one might be led to think that this occurs because there are no people left to infect, but there is much evidence against this explanation. We shall now prove that, in the $S \rightarrow I \rightarrow R$ model, the number of susceptible individuals decreases without ever reaching zero.

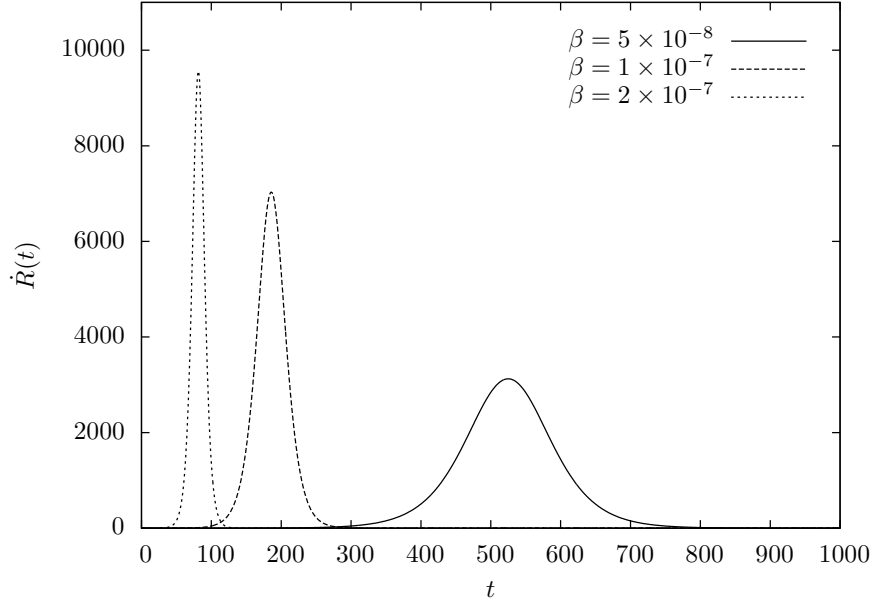


FIGURE 4.5. Epidemic curve in the deterministic $S \rightarrow I \rightarrow R$ model for different values of β and $\gamma = 0.025$; the population is of size $N = 10^6$ and initially a single individual is infective ($\alpha = N^{-1}$).

THEOREM 4.2 (Kermack-McKendrick Survival Theorem). *Let us introduce the following notation,*

$$(4.25) \quad S_\infty = \lim_{t \rightarrow \infty} S(t), \quad I_\infty = \lim_{t \rightarrow \infty} I(t), \quad R_\infty = \lim_{t \rightarrow \infty} R(t).$$

When the disease ultimately ceases spreading, a positive number $S_\infty > 0$ of susceptible individuals remain uninfected.

PROOF. Since $S(t) + I(t) + R(t) = N$ at all time $t > 0$, we have that $R(t) \leq N$ at the same time. Therefore, from Equation 4.18 we have that

$$(4.26) \quad S_\infty = S(0) e^{-\beta R_\infty / \gamma} \geq S(0) e^{-\beta N / \gamma},$$

which shows that $S_\infty > 0$.

An equation for S_∞ can be obtained as follows. Dividing Equation (4.14b) by Equation (4.14a), we get the differential equation

$$(4.27) \quad \frac{dI}{dS} = \frac{\beta S(t) I(t) - \gamma I(t)}{-\beta S(t) I(t)} = -1 + \frac{\gamma}{\beta S(t)},$$

which can be easily integrated, taking into account the initial conditions $S(0)$ and $I(0)$, yielding

$$(4.28) \quad S(t) + I(t) - \frac{\gamma}{\beta} \ln S(t) = S(0) + I(0) - \frac{\gamma}{\beta} \ln S(0).$$

Taking the limit as $t \rightarrow \infty$ and rearranging the terms leads to

$$(4.29) \quad S_\infty = N - \frac{\gamma}{\beta} \ln \frac{S(0)}{S_\infty} \approx N \left(1 - \frac{1}{R_0} \ln \frac{S(0)}{S_\infty} \right),$$

where we have assumed that $R(0) = 0$, so that $S(0) + I(0) = N$, and we have made use of Equation 4.15 and of the fact that $I_\infty = 0$. \square

4.2.3. Other models. The $S \rightarrow I$ and $S \rightarrow I \rightarrow R$ models introduced above are the most simple compartmental models, but are nonetheless crucial as building blocks of more complex models: the $S \rightarrow I \rightarrow R$ model, for example, is already an extension of the simpler $S \rightarrow I$ model (to see this, consider the case $\gamma = 0$).

Possible extensions include new states, as in the $S \rightarrow E \rightarrow I \rightarrow R$ model that allows for “exposed” individuals (E), i.e. individuals in which the disease is latent and manifests itself at a constant rate, as well as the possibility of reinfection, as in the $S \rightarrow I \rightarrow R \rightarrow S$, in which removed individuals regain susceptibility at a constant rate. All these models can be further extended by considering population dynamics (births and deaths, which are commonly considered to occur at the same rate to keep the total population size N constant), and vaccination strategies.

4.3. Stochastic models

In this section we shall introduce, following the presentations of Daley and Gani [13] and Allen [2], some stochastic models in discrete and continuous time that have been proposed in the literature.

As a general remark, it is important to note that, whereas stochastic models have a natural deterministic description that can be obtained by taking expected values of the involved quantities, the reverse does not hold true: starting with a system of differential equations, one can derive a variety of corresponding stochastic models whose deterministic skeleton corresponds to the starting system of differential equations [24].

4.3.1. Chain binomial models. Chain binomial models are among the first discrete time stochastic epidemic models that were studied; as their name implies, they entail sequences of binomially distributed random variables. There are two classic such models: one is due to Reed and Frost and was put forward in their lectures at Johns Hopkins University in 1928, but never published, until Abbey [1] gave a detailed account of it; the other is due to Greenwood [23]. They are both Markov chains, even though this fact was not fully appreciated until the work of Gani and Jerwood [20].

The main assumption behind these models is that the infectious period, i.e. the period during which an individual shows symptoms and is able to infect others, is relatively short compared to the latent period, i.e. the period between infection and appearance of symptoms. Moreover, contacts are considered instantaneous, and the infectious period is concentrated at the contact time. Because of the “short” infectious period, we can identify a class of formerly infective individual that are thus immediately removed; therefore, the infectious period last exactly one unit of time. This assumption also leads to another interesting property: if all initially infective individuals

are simultaneously in the infectious period (as is necessarily the case with a single initially infective individual), the disease will spread in successive generations that do not overlap in time. This characteristic sets this model radically apart from the $S \rightarrow I \rightarrow R$ model of Section 4.2.2, whose great applicability to real-world data may well be due to the possibility of smaller scale overlapping epidemics [13].

Consider the two random variables S_t and I_t with discrete state spaces $\mathcal{S}_S = \mathcal{S}_I = \{0, 1, \dots, N\}$ representing the number of susceptible and infective individuals at time t , respectively. Note that $S_t + I_t = S_{t-1}$. Let us denote by $p \in (0, 1)$ the probability of contact between a susceptible and an infective individual, and by $\beta \in (0, 1)$ the probability that this contact results in infection of the susceptible individual by the infective one. Then, the probability α that there is no infection due to any single infective individual can be expressed as the sum of two probabilities: (a) the probability $(1 - p)$ that no contact with an infective individual occurs; (b) the probability $p(1 - \beta)$ that a contact with an infective individual occurs, but that this contact does not result in infection. Thus, we have that

$$(4.30) \quad \alpha = (1 - p) + p(1 - \beta) = 1 - p\beta.$$

The Greenwood model [23] assumes that the cause of infection is unrelated to the number of infective individuals, so that α is simply the probability of non-infection. In this case, we have that $I_t = S_{t-1} - S_t$, and

$$(4.31) \quad \begin{aligned} & \mathbb{P}[S_{t+1} = s_{t+1}, I_{t+1} = i_{t+1} \mid S_t = s_t, I_t = i_t] \\ &= \binom{s_t}{s_{t+1}} \alpha^{s_{t+1}} (1 - \alpha)^{i_{t+1}} = \binom{s_t}{s_{t+1}} \alpha^{s_{t+1}} (1 - \alpha)^{s_{t+1} - s_t}, \end{aligned}$$

which shows that $\{S_t, t = 0, 1, \dots\}$ is a univariate Markov chain, since I_t fully depends on S_t , and the value of the latter at time $t + 1$ depends only on its value at time t .

The Reed-Frost model [1], on the other hand, considers that a susceptible individual remains so from t to $t + 1$ only if infectious contact with all I_t infective individuals is avoided, which occurs independently for each susceptible individual with probability α^{I_t} . Thus $S_{t+1} \sim \text{Binomial}(S_t, \alpha^{I_t})$, and

$$(4.32) \quad \begin{aligned} & \mathbb{P}[S_{t+1} = s_{t+1}, I_{t+1} = i_{t+1} \mid S_t = s_t, I_t = i_t] \\ &= \binom{s_t}{s_{t+1}} \alpha^{i_t s_{t+1}} (1 - \alpha^{i_t})^{s_t - s_{t+1}}, \end{aligned}$$

which shows that $\{(S_t, I_t), t = 0, 1, \dots\}$ is a bivariate Markov chain, since the values of S_t and I_t at time $t + 1$ depend only on their values at time t .

Since the numbers of infective individuals in successive generations are binomially distributed, it is possible to readily compute their expectations. For the Greenwood model, Equation (4.31) immediately yields

$$(4.33) \quad \mathbb{E}[S_{t+1} \mid S_t] = \alpha S_t,$$

and thus

$$(4.34a) \quad \mathbb{E}[S_t | S_0 = s_0] = \alpha^t s_0,$$

$$(4.34b) \quad \mathbb{E}[I_t | S_0 = s_0] = \alpha^{t-1} (1 - \alpha) s_0.$$

It follows from Equation (4.34a) that $\mathbb{E}[S_t] \rightarrow 0$ as $t \rightarrow \infty$, which means that, since S_t is non-negative, it holds that $S_t = 0$ for all sufficiently large t .

As for the Reed-Frost model, Equation (4.32) yields

$$(4.35) \quad \mathbb{E}[S_{t+1}, I_{t+1} | S_t = s_t, I_t = i_t] = (s_t \alpha^{i_t}, s_t (1 - \alpha^{i_t})).$$

These equations, unlike those we determined for the Greenwood model, do not lead to an explicit solution; however, given their recurrent nature, they can be easily evaluated numerically, as shown in Figure 4.6.

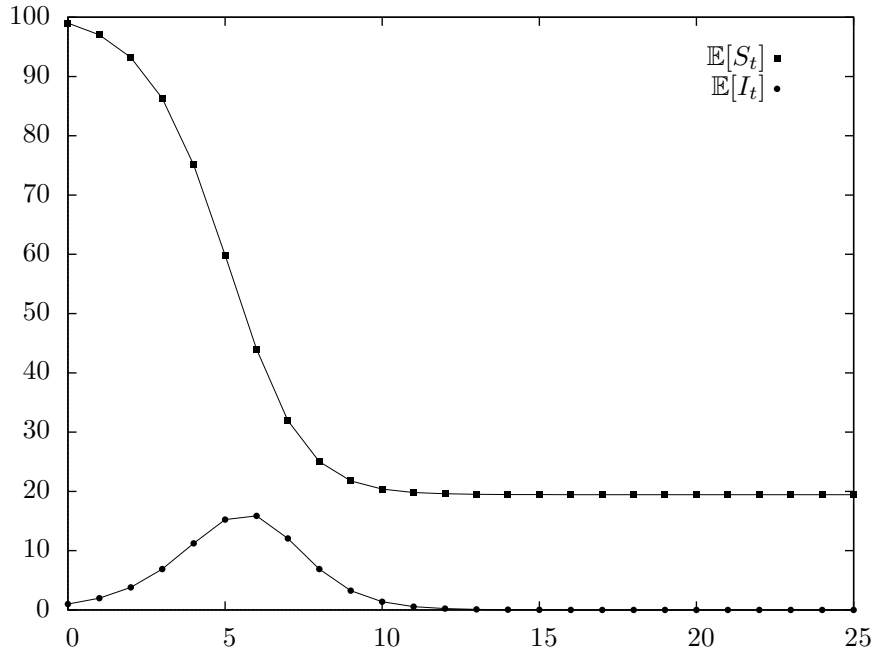


FIGURE 4.6. Evolution of the expected number of susceptible and infective individuals in the Reed-Frost model; the probability of no infection is $\alpha = 0.98$, the population is of size $N = 100$, and initially a single individual is infective.

4.3.2. Continuous time Markov chain. We now move to continuous time Markov chains, which are a natural way to introduce stochasticity into the deterministic $S \rightarrow I \rightarrow R$ model of Section 4.2.

Consider the two random variables $S(t)$ and $I(t)$ with discrete state spaces $\mathcal{S}_S = \mathcal{S}_I = \{0, 1, \dots, N\}$ representing the number of susceptible and infective individuals at time t , respectively. Furthermore, assume that time is continuous, $t \in [0, +\infty)$, and that the population mixes homogeneously, so that infections occur at rate β and recoveries at rate γ .

We can thus define the bivariate Markov process $\{(S(t), I(t)), t \geq 0\}$ with infinitesimal transition probabilities as follows,

$$(4.36) \quad \mathbb{P}[S(t + \Delta_t) = s + \Delta_S, I(t + \Delta_t) = i + \Delta_I \mid S(t) = s, I(t) = i] = \begin{cases} \beta s i \Delta_t + o(\Delta_t) & \Delta_S = -1, \Delta_I = 1, \\ \gamma i \Delta_t + o(\Delta_t) & \Delta_S = 0, \Delta_I = -1, \\ 1 - (\beta s + \gamma) i \Delta_t + o(\Delta_t) & \Delta_S = 0, \Delta_I = 0, \\ o(\Delta_t) & \text{otherwise,} \end{cases}$$

where $o(\Delta_t)$ is such that

$$(4.37) \quad \lim_{\Delta_t \rightarrow 0} \frac{o(\Delta_t)}{\Delta_t} = 0,$$

and we again assumed that Δ_t is sufficiently small that at most a single transition (either $S + I \rightarrow 2I$ or $I \rightarrow R$) occurs. The possible states and transitions among them are schematized in Figure 4.7.

Writing the state probabilities as follows,

$$(4.38) \quad p_{(s,i)}(t) = \mathbb{P}[S(t) = s, I(t) = i \mid S(0) = s_0, I(0) = i_0],$$

where $s_0 \in \mathcal{S}_S$, $i_0 \in \mathcal{S}_I$ are the initial number of susceptible and infective individuals, respectively, and $s_0 + i_0 \leq N$, we have that

$$(4.39a) \quad p_{(s_0,i_0)}(t + \Delta_t) = [1 - (\beta s_0 + \gamma) i_0 \Delta_t] p_{(s_0,i_0)}(t) + o(\Delta_t),$$

$$(4.39b) \quad \begin{aligned} p_{(s,i)}(t + \Delta_t) &= \beta (s + 1) (i - 1) \Delta_t p_{(s+1,i-1)}(t) \\ &+ \gamma (i + 1) \Delta_t p_{(s,i+1)}(t) \\ &+ [1 - (\beta s + \gamma) i \Delta_t] p_{(s,i)}(t) + o(\Delta_t), \end{aligned}$$

since, as shown in Figure 4.8, the probability of being in state (s, i) at time $t + \Delta_t$ can be written by the Markov property as the sum of: (a) the probability of being in state $(s + 1, i - 1)$ at time t and that the transition that occurred was $S + I \rightarrow 2I$; (b) the probability of being in state $(s, i + 1)$ at time t and that the transition that occurred was $I \rightarrow R$; (c) the probability of being in state (s, i) at time t and that no transition occurred.

Subtracting $p_{(s_0,i_0)}(t)$ on both sides of Equation (4.39a) and $p_{(s,i)}(t)$ on both sides of Equation (4.39b), dividing by Δ_t and taking the limit as $\Delta_t \rightarrow 0$ leads to the following system of forward Kolmogorov differential equations,

$$(4.40a) \quad \frac{dp_{(s_0,i_0)}}{dt} = -(\beta s_0 + \gamma) i_0 p_{(s_0,i_0)}(t),$$

$$(4.40b) \quad \begin{aligned} \frac{dp_{(s,i)}}{dt} &= \beta (s + 1) (i - 1) p_{(s+1,i-1)}(t) \\ &+ \gamma (i + 1) p_{(s,i+1)}(t) \\ &- (\beta s + \gamma) i p_{(s,i)}(t), \end{aligned}$$

for $0 \leq s \leq s_0$, $0 \leq i \leq s_0 + i_0$ and $0 \leq s + i \leq s_0 + i_0$, subject to the initial conditions $p_{(s_0,i_0)}(0) = 1$ and $p_{(s,i)}(0) = 0$ otherwise, $(s, i) \neq (s_0, i_0)$.

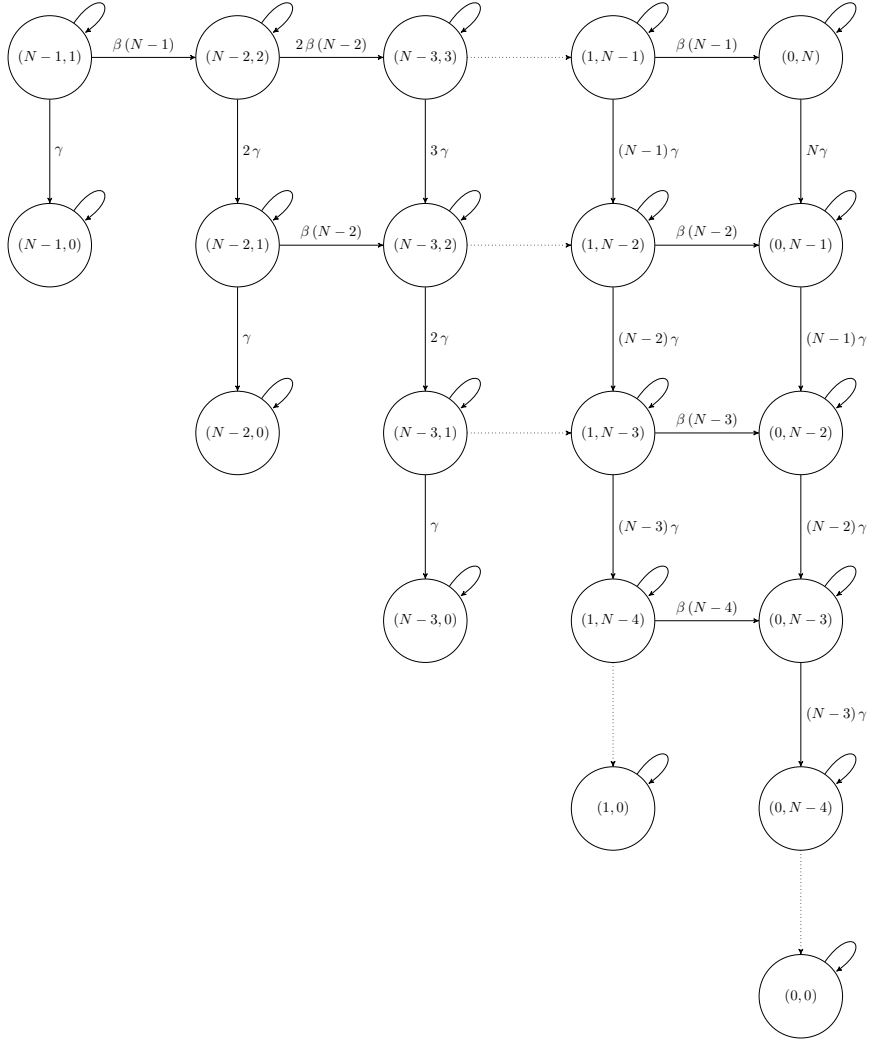


FIGURE 4.7. Bivariate Markov chain $S \rightarrow I \rightarrow R$ model: each state in the chain is characterized by a couple (S, I) representing the number of susceptible individuals S and that of infective individuals I ; the initial state depends on the initial conditions, but is usually assumed to be $(N-1, 1)$; note that all states with $I = 0$ are absorbing.

We next present a threshold theorem, similar to Theorem 4.1, for the stochastic $S \rightarrow I \rightarrow R$ model.

THEOREM 4.3 (Whittle's Threshold Theorem). *For any $\alpha \in (0, 1)$, let $\pi(\alpha)$ denote the probability that the proportion of susceptible individuals that are ever infected, i.e. the intensity of the epidemic, does not exceed α . It*

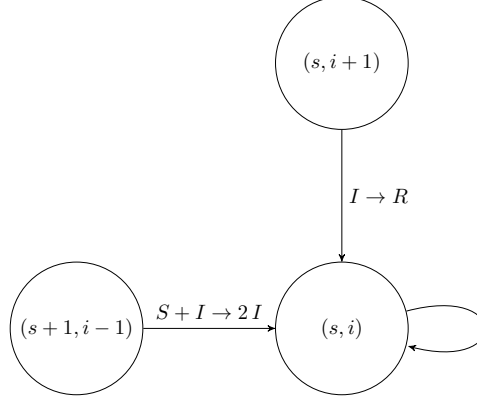


FIGURE 4.8. Possible transitions in the bivariate Markov chain $S \rightarrow I \rightarrow R$ model during the infinitesimal time interval $(t, t + \Delta_t)$.

holds that

$$(4.41a) \quad \text{if } R_0 \leq 1, \text{ then } \pi(\alpha) = 1,$$

$$(4.41b) \quad \text{if } 1 < R_0 \leq \frac{1}{1-\alpha}, \text{ then } \left(\frac{1}{R_0}\right)^{I(0)} \leq \pi(\alpha) \leq 1,$$

$$(4.41c) \quad \text{if } R_0 > \frac{1}{1-\alpha}, \text{ then } \left(\frac{1}{R_0}\right)^{I(0)} \leq \pi(\alpha) \leq \left(\frac{1}{(1-\alpha)R_0}\right)^{I(0)}.$$

PROOF. The proof of Theorem 4.3 can be found, for example, in [13, Ch. 3]; the original result is due to Whittle [43]. The basic idea behind the proof is to bound the component $I(t)$ between two birth-death processes. \square

REMARK 4.1. For $R_0 \leq 1$, we have that the probability that the epidemic achieves an intensity greater than any $\alpha \in (0, 1)$ is zero. This result is strikingly similar to that of Theorem 4.1 for the deterministic $S \rightarrow I \rightarrow R$ model, which predicted that no epidemic would occur for $R_0 \leq 1$.

On the other hand, for $R_0 > 1$, we have that the probability that the epidemic exceeds an intensity $\alpha \in (0, 1)$ for small α is approximately equal to $1 - (1/R_0)^{I(0)}$, whereas in the deterministic $S \rightarrow I \rightarrow R$ model this situation would always lead to an epidemic.

CHAPTER 5

Epidemics on networks

Graphs are extremely flexible and powerful modelling tools for representing elements of a complex system and relations between them. In the field of epidemic modelling, they have found two main uses: (a) as a structural enhancement to classic models that consider the population to mix homogeneously; (b) as an extension of classic models to multiple populations, by providing the coupling among them.

The first kind of use gave rise to population models, in which each vertex represents an individual, and edges represent contacts it has with other members of the population. The disease is assumed to spread only along edges, with the probability of a susceptible vertex becoming infective proportional to the number of its infective neighbours. An important issue that population models need to deal with is the fact that precise information about real-world contact networks is very difficult to obtain and is often affected by severe sampling biases. For this reason, most models consider ensembles of networks characterized by at most a few parameters, and derive average results for the ensemble instead. In this context, graphs are mostly assumed to be binary, under the assumption that population structure (as described by the edges and captured by the parameters) determines the outcome of the spreading process far more than the strength of interactions.

The second application resulted in meta-population models, in which each vertex represents a population, and edges represent interactions among them, usually in the form of travel events. For this reason, graphs used in these models are usually transportation networks, possibly at different scales, and are thus frequently weighted as well as directed. It must also be noted that, apart from the coupling imposed by this network, the disease evolves almost independently inside each population, most commonly according to one of the models introduced in Chapter 4.

5.1. Population models

As the name suggests, population models consider disease spreading at the level of individuals belonging to a single population. In this context, each vertex represents a single individual and may be in any of the considered states, and edges represent pairwise interactions between individuals that may result in transmission of the disease. If the graph is complete, each individual is in the position of becoming infective and infecting every other, so that these more complex models reduce to those presented in Chapter 4.

As outlined in the introduction to this chapter, since accurate, real-world network data is rarely available, population models usually assume some structural properties and derive results under these assumptions. These properties are mostly taken into account by parametrizing the model, so that results will apply to ensembles of graphs rather than single instances.

A model that has been extensively studied is that of Erdős and Rényi [19], in which the presence of each edge is independent of that of all others and occurs with a given probability equal for all edges, leading to a Poisson degree distribution in the limit of large graphs. A generalization of this model, called the configuration model (see [36] and references therein), can be used to construct random graphs that are characterized only by an arbitrary degree distribution.

One of the first population models proposed in the literature, due to Newman [35] (see also [37, Ch. 17]), considers epidemics occurring in a deterministic setting on a random graph with arbitrary degree distribution. In his work, Newman generalizes the deterministic $S \rightarrow I \rightarrow R$ model by introducing two modifications: (a) the contact network limiting the spreading process and parametrized by its degree distribution; (b) a varying probability of disease transmission along each edge that can thus be considered its weight. The author then proceeds to show that varying transmission probabilities do not affect the spreading process, and can be substituted by a single quantity named “transmissibility”. As for the first modification, he further derives exact results for random networks with arbitrary degree distributions, giving expressions for the outbreak size distribution and arriving at the critical transmissibility value above which epidemics occur.

This model can be made more realistic by considering random correlated graphs, which are random graphs completely defined by their degree distribution and, for each possible degree, the conditional degree distribution for neighbours of vertices with that degree. Even in this case it is possible to compute the epidemic threshold, i.e. the critical value above which epidemics occur; in particular, Boguñá et al. [7] did so for the deterministic $S \rightarrow I \rightarrow S$ and $S \rightarrow I \rightarrow R$ models.

5.2. Meta-population models

Meta-population models are among the simplest and most applicable spatial models for many human diseases [26, Ch. 7]. They consider different populations of variable size (also called patches), within which the disease evolves almost independently, that are coupled by means of a network representing fluxes of individuals travelling among them. An example of such a model is shown in Figure 5.1. It should be noted that, in contrast to population models, reliable data for population sizes and transportation networks is far easier to obtain, and is often made available and kept updated by national and international statistical services. The model that we present

stems from Soviet work on modelling geographic spread of influenza in the former Union of Soviet Socialist Republics [32, 40].

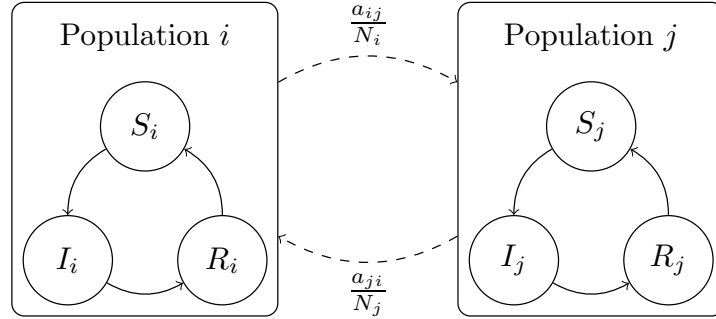


FIGURE 5.1. Example of a meta-population model: each population has an associated size N_i , N_j ; the number of passengers per unit time from population i to population j is denoted a_{ij} , and the associated travel probability is given by $p_{ij} = a_{ij}/N_i$. Note that this probability is generally different from the travel probability in the opposite direction, $p_{ji} = a_{ji}/N_j$. Internally, each population is assumed to behave as an $S \rightarrow I \rightarrow R \rightarrow S$ model.

Because of the way they are defined, meta-population models naturally build upon models that consider a single population, so that their description can usually be limited to the additional terms added to account for travels. This is the approach we shall follow in the following sections.

DEFINITION 5.1 (Travel probability). The probability p_{ij} of travelling from population i to population j , $j \neq i$, is defined as follows,

$$(5.1) \quad p_{ij} = \frac{a_{ij}}{N_i},$$

where a_{ij} is the number of travellers in that direction per unit time, and N_i is the size of population i .

REMARK 5.1. The travel probabilities $\{p_{ij}, i \neq j\}$ implicitly define a directed weighted graph that incorporates information about the transportation network as well as about the population sizes.

5.2.1. Deterministic models. To see how the meta-population concept can be applied to deterministic models, let us present a way of introducing coupling among different populations.

DEFINITION 5.2 (Transportation coupling). Given a meta-population model with k populations and travel probabilities $\{p_{ij}, i, j = 1, \dots, k, i \neq j\}$, and denoting by X_i the number of individuals in state $X = S, I, R, \dots$ in population $i = 1, \dots, k$, we can introduce coupling among these quantities

by considering the following substitution for $i = 1, \dots, k$,

$$(5.2) \quad X_i \rightsquigarrow X_i + \sum_{j \neq i} \left(\underbrace{p_{ji} X_j}_{(a)} - \underbrace{p_{ij} X_i}_{(b)} \right).$$

In the expression above, fixing a state $X = S, I, R, \dots$ and a population $i = 1, \dots, k$, we have that: (a) represents individuals in the same state travelling to population i from any other population $j \neq i$; (b) represents individuals in the same state travelling from population i to any other population $j \neq i$. In both cases, travels are mediated by the travel probabilities, which might be zero to indicate that no direct connection exists between the two populations involved.

As an example, consider a simple $S \rightarrow I$ model with only two populations. If the two populations were not coupled, we would have a simple system of independent ordinary differential equations,

$$(5.3a) \quad \frac{dI_1}{dt} = \beta (N_1 - I_1(t)) I_1(t),$$

$$(5.3b) \quad \frac{dI_2}{dt} = \beta (N_2 - I_2(t)) I_2(t),$$

which could be easily solved given suitable initial conditions $I_1(0)$ and $I_2(0)$. If we assume that travel probabilities are small, so that changes in population sizes due to travels are negligible, taking into account the coupling between the two populations yields instead the following system of coupled ordinary differential equations,

$$(5.4a) \quad \frac{dI_1}{dt} = \beta (N_1 - I_1(t)) I_1(t) + p_{21} I_2(t) - p_{12} I_1(t),$$

$$(5.4b) \quad \frac{dI_2}{dt} = \beta (N_2 - I_2(t)) I_2(t) + p_{12} I_1(t) - p_{21} I_2(t),$$

together with initial conditions $I_1(0)$ and $I_2(0)$. This substitution can be easily carried out for models that include more populations as well as more states, but will generally yield system of differential equations whose solution can only be determined numerically.

5.2.2. Stochastic case. Stochastic models can also be extended to multiple populations. For discrete time models, the following definition gives the probability distribution of the number of outgoing travellers from a fixed population i to any other population $j \neq i$ it is connected to.

PROPOSITION 5.1 (Probability distribution of the number of outgoing travellers for a fixed population). *Let us denote by $X_i(t)$ the random variable representing the number of individuals in state $X = S, I, R, \dots$ in population i at time t , and by $X_{ij}(t)$ the random variable representing the number of such individuals travelling from population i to population j , $j \neq i$, or staying in population i , $i = j$. Then, for a fixed population i , the random variables $\{X_{ij}(t)\}$ are distributed according to a multinomial distribution with*

$X_i(t)$ trials and probabilities given by the travel probabilities $\{p_{ij}, j \neq i\}$, together with the probability $p_{ii} = 1 - \sum_{j \neq i} p_{ij}$ of staying in population i .

As for continuous time Markov chains, let us consider again a simple $S \rightarrow I$ model with only two populations. If we again assume that travel probabilities are small, so that changes in population sizes due to travels are negligible, this situation can be modelled by means of a bivariate Markov process $\{(I_1(t), I_2(t)), t \geq 0\}$ with infinitesimal transition probabilities as follows,

$$(5.5) \quad \mathbb{P}[I_1(t + \Delta_t) = i_1 + \Delta_1, I_2(t + \Delta_t) = i_2 + \Delta_2 \mid I_1(t) = i_1, I_2(t) = i_2] = \begin{cases} \beta s_1 i_1 \Delta_t + o(\Delta_t) & \Delta_1 = 1, \Delta_2 = 0, \\ \beta s_2 i_2 \Delta_t + o(\Delta_t) & \Delta_1 = 0, \Delta_2 = 1, \\ p_{12} i_1 \Delta_t + o(\Delta_t) & \Delta_1 = -1, \Delta_2 = 1, \\ p_{21} i_2 \Delta_t + o(\Delta_t) & \Delta_1 = 1, \Delta_2 = -1, \\ 1 - [(\beta s_1 + p_{12}) i_1 + (\beta s_2 + p_{21}) i_2] \Delta_t & \Delta_1 = 0, \Delta_2 = 0, \\ o(\Delta_t) & \text{otherwise,} \end{cases}$$

where $s_j = N_j - i_j$, $j = 1, 2$, and $o(\Delta_t)$ is such that

$$(5.6) \quad \lim_{\Delta_t \rightarrow 0} \frac{o(\Delta_t)}{\Delta_t} = 0,$$

and we assumed that Δ_t is sufficiently small that at most a single transition (either the infection of a susceptible individual in one of the two populations or a travel between them) occurs. The possible transitions are schematized in Figure 5.2.

The number of possible states in Markov chains built using this methods, however, can easily grow very large, making it difficult to accurately simulate from them.

As referred at the beginning of this section, meta-populations models were used to model geographic spread of influenza in the former U.S.S.R. [32, 40]. More recently, Colizza et al. [12] considered a similar approach that, however, also incorporates stochastic elements, to model worldwide spread of influenza using actual information about transportation networks at different scales [3, 11]. This modelling effort ultimately resulted in a computational model [4] and a publicly available software [41].

Finally, it must be noted that many other models, often incorporating stochasticity, have been developed to determine the rate of spatial spread of a disease and devise targeted control measures that consider its local nature. The interested reader is referred to the book by Keeling and Rohani [26, Ch. 7].

As we shall see in the following chapter, meta-populations models offer the possibility of an interesting estimation approach for the infection rate β : indeed, it turns out that this crucial parameter can be inferred from knowledge of the arrival time of the first infective individual in each population.

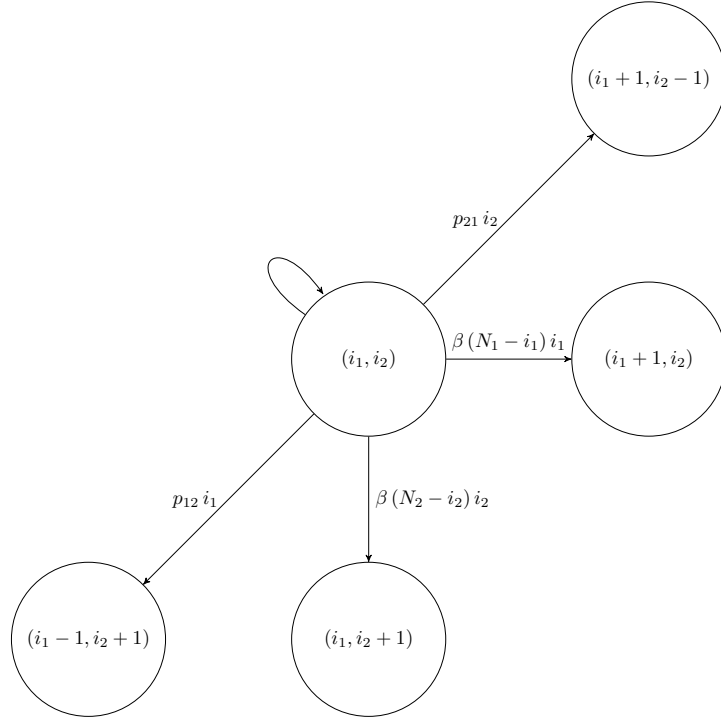


FIGURE 5.2. Possible transitions in the bivariate Markov chain $S \rightarrow I$ meta-population model with two populations during the infinitesimal time interval $(t, t + \Delta_t)$.

CHAPTER 6

Estimation of the infection rate from arrival times

Accurate predictions of future epidemics by mathematical models clearly depend on selection of appropriate values for their parameters, which in turn must proceed from empirical data.

The most difficult (and probably the most important) parameter to estimate is the infection rate β : as we saw in Chapter 4, this is the only parameter in the $S \rightarrow I$ model, and a crucial component of the $S \rightarrow I \rightarrow R$ model, since the recovery rate γ can be inferred much more easily by means of clinical observation.

In this context, meta-population models lend themselves to an interesting estimation approach, originally introduced by Gautreau et al. [21]: if the disease is not endemic, but is initially present in a single population from which it spreads by means of travels, we can infer the infection rate β from the arrival times of the first infective individual in other populations that were, up to that moment, wholly composed of susceptible individuals. It is easy to understand that these two quantities are inversely correlated: larger values of β correspond to earlier arrival times, since it takes less time for the disease to develop in the first population and reach that “critical mass” that corresponds to a non-negligible travel probability for infective individuals. As we shall see in the following sections, the infection rate β is indeed the only unknown parameter of the probability distribution of the arrival times, which in turn makes its estimation possible. We note that, in this context, populations are considered quite large and only a few individuals are assumed to travel, leading to small travel probabilities; this is the case, for example, of air travel [11].

In the rest of this chapter we shall therefore be concerned with the problem of estimating the infection rate β from this kind of data. This will be done by deriving the probability distribution of the arrival times in a number of scenarios: in particular, in Section 6.1 we will derive the probability distribution of the arrival time of the first infective individual in the second of two populations; this result will then be extended to a line of k populations in Section 6.2, and to a general network of populations in Section 6.3. As said, all these result will include the infection rate β as the only unknown parameter. Finally, in Section 6.4, we will outline how to obtain maximum-likelihood estimates for β using these results, and show the accuracy of the proposed estimation method by means of a number of computer simulations.

6.1. Distribution of the arrival time with two populations

Consider a graph with only two vertices, representing populations of sizes N_1 and N_2 , linked by two directed edges with weights a_{12} and a_{21} that represent the number of travellers per unit time from the first to the second population and *vice versa*, respectively. Additionally, assume that each population encloses a simple $S \rightarrow I$ model, and that initially ($t = 0$) the only infective individual belongs to the first population, $I_1(0) = 1$, and $I_2(0) = 0$. Travels are assumed to occur independently; the probabilities of travelling between the two populations are

$$(6.1) \quad p_{12} = \frac{a_{12}}{N_1} \quad \text{and} \quad p_{21} = \frac{a_{21}}{N_2}.$$

The situation is depicted in Figure 6.1.

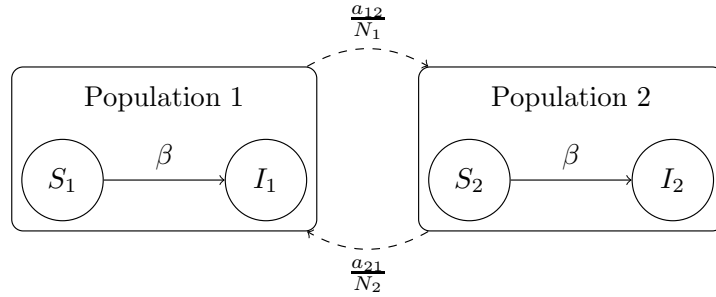


FIGURE 6.1. Meta-population model with two populations; each populations encloses an $S \rightarrow I$ model.

We are interested in computing the probability distribution of the time of travel of the first infective individual from the first to the second population, denoted T_{12}^* . In the following sections, we shall introduce three possible approaches to do this. In the first two approaches, we will consider that travels are the only stochastic events, while infections follow a deterministic model; using the theory of non-homogeneous Poisson processes, we will derive simple analytic expressions for the cumulative distribution function and probability density function of T_{12}^* , and later show them to be similar to the approximate derivation of Gautreau et al. [21]. Then, we will consider a doubly stochastic model in which both infections and travels are stochastic events; while possibly more realistic, this model leads to complicated equations and cannot be easily extended to the case of k populations, as we do for the first approach in Section 6.2.

6.1.1. First arrival time in a non-homogeneous Poisson process.

In this first approach we will consider that travels are the only stochastic events, while infections follow a deterministic model. The process of arrivals of infective individuals at the second population satisfies the conditions for being a non-homogeneous Poisson process given in Definition 2.10, since:

- (1) by assumption, the initial number of infective individuals in the second population is zero;
- (2) by assumption, travels (and thus increments) are independent;
- (3) the probability that a single individual will travel to the second population during a suitably small time interval Δ_t is given by the number of infective individuals in the first population multiplied by the probability of travelling to the second population; moreover, since the number of infective individuals varies over time, this rate is also time-dependent;
- (4) since, by assumption, travels are independent, the probability that more than one individual will travel to the second population during a suitably small time interval Δ_t is negligible.

The time-dependent rate is thus given by

$$(6.2) \quad \lambda(t) = p_{12} I_1(t),$$

where I_1 is given by Equation (4.8) correctly parametrized,

$$(6.3) \quad I_1(t) = \frac{N_1}{1 + (N_1 - 1) e^{-\beta N_1 t}}.$$

Moreover, if we assume that the first travel occurs in the first stage of the epidemic, we can introduce the following approximation,

$$(6.4) \quad I_1(t) \approx e^{\beta N_1 t},$$

which is of particular interest since it can also be used when considering that each population encloses an $S \rightarrow I \rightarrow R$ model, for which no analytic expression for $I(t)$ exists [21]. Figure 6.2 exemplifies the agreement between Equation (6.3) and the approximation of Equation (6.4), which rapidly becomes non-existent as t gets larger and larger.

Using this approximation, it is easy to see that the time-dependent rate $\lambda(t)$ has exponential form,

$$(6.5) \quad \lambda(t) \approx p_{12} e^{\beta N_1 t},$$

and thus, by Corollary 2.4, we have that

$$(6.6) \quad T_{12}^* \sim \Lambda^+ \left(-\frac{1}{\beta N_1} \ln \frac{p_{12}}{\beta N_1}, \frac{1}{\beta N_1} \right),$$

which shows that the infection rate β is indeed a parameter of the probability distribution of the first arrival time T_{12}^* . A plot of the associated probability density function for different values of the travel probability p_{12} is shown in Figure 6.3; as we would expect, larger values of p_{12} lead to a shift of the probability density function of the first arrival time T_{12}^* towards smaller values. Figure 6.4 shows the same function for different values of the infection rate β ; understandably, larger values of β also lead to a shift of the probability density function of T_{12}^* towards smaller values. Finally, we note

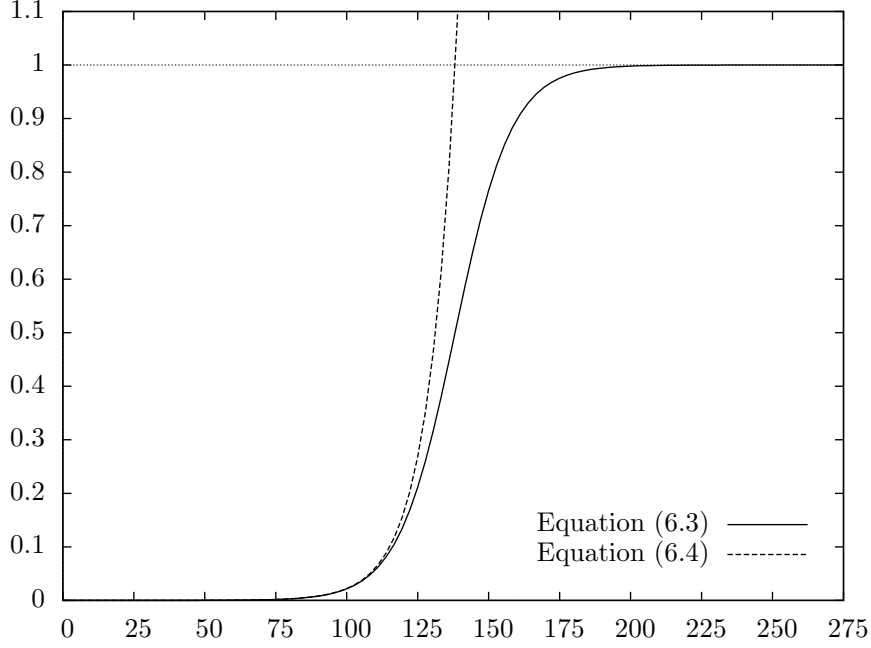


FIGURE 6.2. Approximation of Equation (6.3) by the simpler function of Equation (6.4) for $N_1 = 10^6$ and $\beta = 10^{-7}$; to improve readability, the vertical axis has been rescaled by multiplying values by N_1^{-1} .

that plots of the slightly more complicated function obtained using Equation (6.3) instead of the approximation of Equation (6.4) match perfectly the presented plots.

6.1.2. Gumbel approximation of Gautreau et al. [21]. In this second approach, which is due to Gautreau et al. [21], we will again consider that travels are the only stochastic events, while infections follow a deterministic model; furthermore, we will assume that time is discretized into intervals of unitary length, and that travels occur instantaneously. The probability of the event $T_{12}^* = t$ can thus be divided into the product of the probabilities of two independent events, namely: (a) at least one infective individual travelling at time t ; (b) no infective individual having travelled at any previous time point $i = 0, 1, \dots, t-1$. Therefore, we have that the probability mass function of T_{12}^* is given by

$$(6.7) \quad \mathbb{P}[T_{12}^* = t] = \underbrace{\left(1 - (1 - p_{12})^{I_1(t)}\right)}_{(a)} \times \underbrace{\prod_{i=0}^{t-1} (1 - p_{12})^{I_1(i)}}_{(b)},$$

where $I_1(t)$ is the number of infective individuals in the first population at time t . The above equation can be conveniently rewritten as follows,

$$(6.8) \quad \mathbb{P}[T_{12}^* = t] = \left(1 - (1 - p_{12})^{I_1(t)}\right) (1 - p_{12})^{\sum_{i=0}^{t-1} I_1(i)}.$$

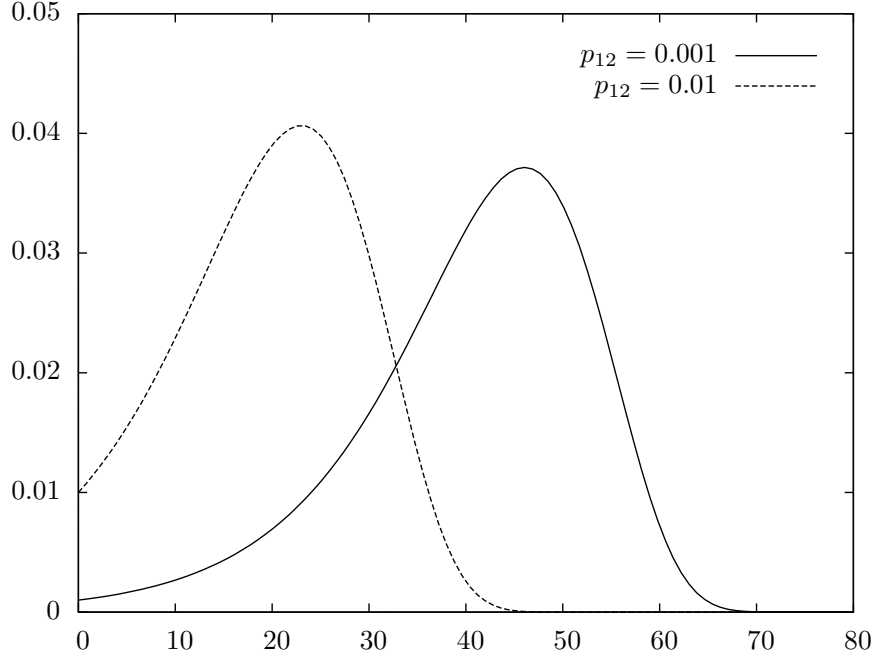


FIGURE 6.3. Probability density function of T_{12}^* as given by Equation (6.6) for different values of p_{12} ; the infection rate is $\beta = 10^{-7}$ and the first population has size $N_1 = 10^6$.

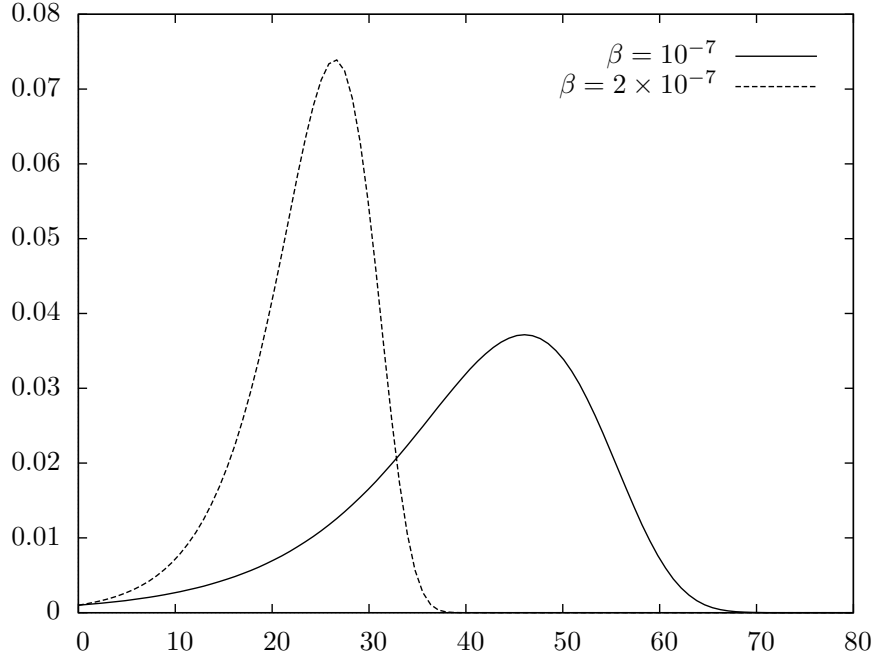


FIGURE 6.4. Probability density function of T_{12}^* as given by Equation (6.6) for different values of β ; the travel probability is $p_{12} = 0.001$ and the first population has size $N_1 = 10^6$.

In the limit of infinitesimal time intervals, Equation (6.8) turns into the probability density function $f_{12}^*(t)$ of T_{12}^* ,

$$(6.9) \quad f_{12}^*(t) = \left(1 - (1 - p_{12})^{I_1(t)}\right) (1 - p_{12})^{\int_0^t I_1(\tau) d\tau}.$$

Assuming that the travel probability p_{12} is small and taking the first-order Taylor approximation around $p_{12} = 0$ for the first factor yields

$$(6.10) \quad \left(1 - (1 - p_{12})^{I_1(t)}\right) \approx p_{12} I_1(t),$$

while for the second factor we obtain

$$(6.11) \quad \begin{aligned} (1 - p_{12})^{\int_0^t I_1(\tau) d\tau} &= \exp\left[\ln\left((1 - p_{12})^{\int_0^t I_1(\tau) d\tau}\right)\right] \\ &= \exp\left(\ln(1 - p_{12}) \int_0^t I_1(\tau) d\tau\right) \\ &\approx \exp\left(-p_{12} \int_0^t I_1(\tau) d\tau\right). \end{aligned}$$

Substituting back into Equation (6.9), we have

$$(6.12) \quad f_{12}^*(t) \approx p_{12} I_1(t) e^{-p_{12} \int_0^t I_1(\tau) d\tau} = \lambda(t) e^{-\int_0^t \lambda(\tau) d\tau},$$

where $\lambda(t)$ is defined as in Equation (6.2). At this point, Gautreau et al. fail to notice that, by Lemma 2.1, the above expression is the probability density function of the first arrival in a non-homogeneous Poisson process with time-dependent rate $\lambda(t)$, and introduce instead the approximation of Equation 6.5, concluding however that T_{12}^* is distributed according to a standard Gumbel distribution truncated for negative values,

$$(6.13) \quad T_{12}^* \sim \Lambda\left(-\frac{1}{\beta N_1} \ln \frac{p_{12}}{\beta N_1}, \frac{1}{\beta N_1}\right), \quad T_{12}^* \geq 0.$$

This approach has a serious drawback: to make sure that the probability density functions still integrates to one over its whole domain, one must require that the probability of negative values is negligible,

$$(6.14) \quad F_{12}^*(0) = 1 - e^{-\frac{1}{\beta N_1} p_{12}} \rightarrow 0,$$

which, for fixed β and N_1 , holds for $p_{12} \rightarrow 0$, i.e. when the number of travellers in the first population is small with respect to its size. The effect of this hypothesis on the goodness of the approximation is exemplified in Figure 6.5; as shown, the difference between the approximated and the actual curve becomes more definite as p_{12} moves away from zero.

6.1.3. Continuous time Markov chain. In this third and final approach, we shall consider a doubly stochastic model in which both infections and travels occur stochastically. While this model can be considered more realistic, it does not lead to simple expressions as those derived so far; moreover, its extension to the case of k populations is not as straightforward as in the first approach we presented, which is why we shall not consider it again in the following sections. Nonetheless, it is important to understand

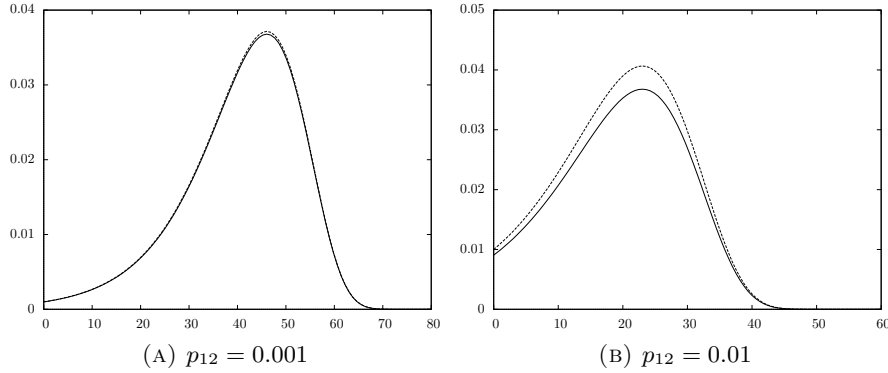


FIGURE 6.5. Effect of the hypothesis $p_{12} \rightarrow 0$ on the truncated Gumbel distribution derived by Gautreau et al. [21]; the solid line shows the probability density function of T_{12}^* as given by Equation (6.13); the correct result, given by Equation (6.6), is also shown for comparison as a dashed line. The infection rate is $\beta = 10^{-7}$ and the first population has size $N_1 = 10^6$.

the differences between the two approaches at least in the simpler case of just two populations, especially because simulations used to validate our method in Section 6.4 are from this doubly stochastic model. For this reason, in what follows we derive the probability density function of T_{12}^* for this kind of model.

To do so, let us recast the problem into that of computing the probability density function for the time until absorption of a Markov chain built so that this time corresponds to the time of the first travel of an infective individual from the first to the second population. Given a first population of size N_1 , our chain thus has $N_1 + 1$ states: N_1 represent the number of infective individuals in the first population, whereas the final absorbing state represents the first travel of an infective individual from that population to the second one. The Markov chain we have just described is depicted in Figure 6.6.

To compute the time until absorption of this Markov chain, let us denote by $q_i(t)$, $i = 1, \dots, N_1$, the probability that, starting from state i , the chain will be absorbed exactly by time t . Making use of the Markov property, we have that the probability of absorption at time $t + \Delta_t$ equals: (a) if $t = 0$, the probability that absorption, and thus the first travel of an infective individual from the first to the second population, occurs during Δ_t ; (b) if $t > 0$, the probability that a new infection occurs during Δ_t , if there are still susceptible individuals, or that no transition occurs at all. Therefore,

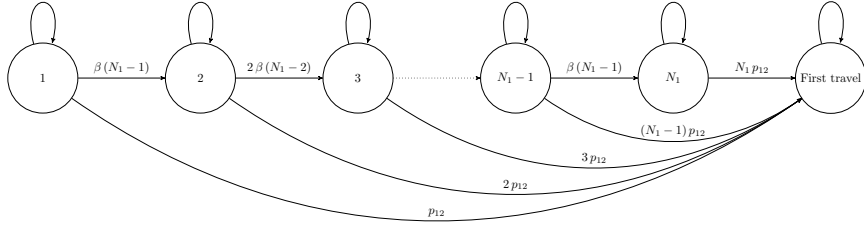


FIGURE 6.6. Markov chain used to compute the probability distribution of the time of the first travel in a meta-population $S \rightarrow I$ model with two populations: all states but the last are characterized by the number I_1 of infective individuals in the first population; the last state corresponds to the first travel and is absorbing. Thus, the probability distribution of the time of the first travel corresponds to that of the time until absorption.

we can write the infinitesimal transition probabilities as follows,

$$(6.15) \quad q_i(t + \Delta_t) = \begin{cases} p_{12} i + o(\Delta_t) & t = 0, \\ \beta(N_1 - i) i \Delta_t q_{i+1}(t) + [1 - (\beta(N_1 - i) + p_{12}) i \Delta_t] q_i(t) + o(\Delta_t) & t > 0, \end{cases}$$

where we assumed that Δ_t is sufficiently small that at most a single transition (either $S + I \rightarrow 2I$ or the first travel) occurs, that $o(\Delta_t)$ is such that

$$(6.16) \quad \lim_{\Delta_t \rightarrow 0} \frac{o(\Delta_t)}{\Delta_t} = 0,$$

that $q_i(0) = 0$ for all $i = 1, \dots, N_1$, and that $q_{N_1+1}(t) = 0$ for all t .

Subtracting $q_i(t)$ on both sides of Equation (6.15), dividing by Δ_t and taking the limit as $\Delta_t \rightarrow 0$ leads to the following system of forward Kolmogorov differential equations,

$$(6.17) \quad \frac{dq_i}{dt} = \beta(N_1 - i) i q_{i+1}(t) - (\beta(N_1 - i) + p_{12}) i q_i(t), \quad i = 1, \dots, N_1,$$

which can be solved exactly, together with the initial conditions $q_i(0) = p_{12} i$, $i = 1, \dots, N_1$, starting from $q_{N_1}(t)$.

The function $q_1(t)$, a plot of which is shown in Figure 6.7, is of particular interest, as it represents the probability density function of the random variable T_{12}^* in the case of a single initially infective individual. The dissimilarity between $q_1(t)$ and the non-negative Gumbel distribution of Equation (6.6) arises from the different nature of the underlying infection process; as we shall understand better in Section 6.4, however, this dissimilarity has little influence on the accuracy of the proposed estimation method.

Finally, we note that, since the time until absorption of a Markov chain like the one depicted in Figure 6.6 follows a phase-type distribution (see Definition 2.8), the same result could have been obtained by observing that

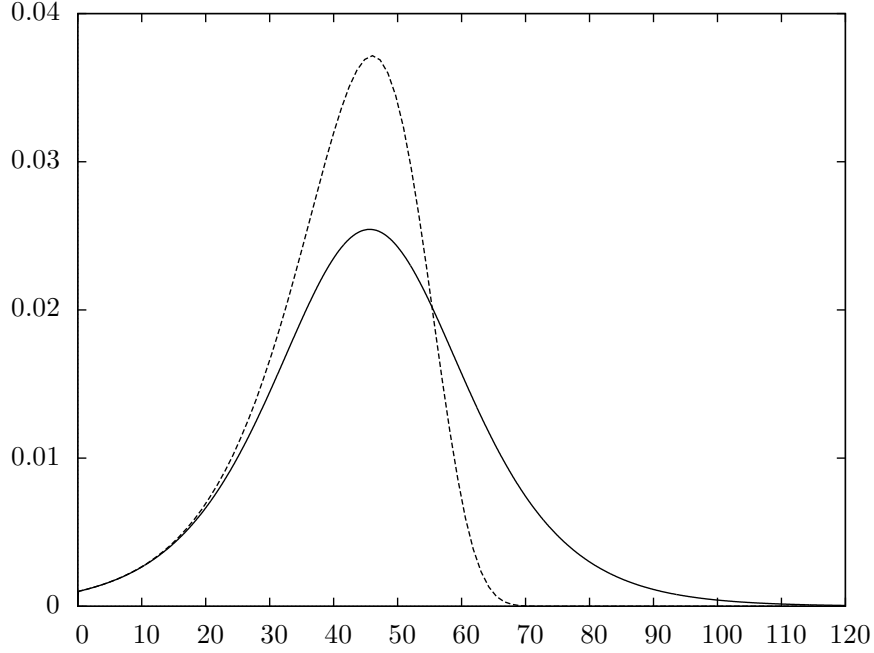


FIGURE 6.7. Probability density function of T_{12}^* obtained as the probability of absorption $q_1(t)$ for a population of size $N_1 = 10^4$, $\beta = 10^{-5}$ and $p_{12} = 0.001$; the probability density function of the non-negative Gumbel distribution of Equation (6.6) is also shown (as a dashed line) for comparison.

$T_{12}^* \sim \text{PH}(\alpha, \mathbf{T})$, where α is a row vector of dimension $N_1 + 1$ whose first entry is equal to one and all other to zero, and the only non-zero elements of the square matrix $\mathbf{T} = (t_{ij})$ of order N_1 are

$$(6.18a) \quad t_{ii} = -(\beta(N_1 - i) + p_{12})i,$$

$$(6.18b) \quad t_{i,i+1} = \beta(N_1 - i)i,$$

for $i = 1, \dots, N_1 - 1$, and $t_{N_1 N_1} = -p_{12}i$. Unfortunately, this approach does not lead to a simpler expression for the probability density function of T_{12}^* , which must still be evaluated numerically, but can be used to easily evaluate its moments.

6.2. Distribution of the arrival time with k populations in a line

Consider now a situation similar to the one introduced above, but with k populations arranged in a line instead of just two. The number of travellers from population i to population j is again denoted by a_{ij} , and the travel probability in the same direction is given by

$$(6.19) \quad p_{ij} = \frac{a_{ij}}{N_i}.$$

As before, initially the only infective individual belongs to the first population, $I_1(0) = 1$, and $I_2(0) = I_3(0) = \dots = I_k(0) = 0$. The situation is depicted in Figure 6.8.

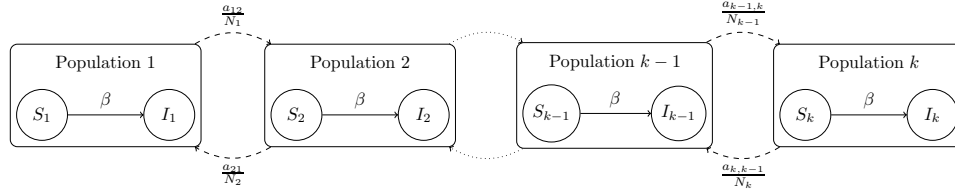


FIGURE 6.8. Meta-population model with k populations arranged in a line; each population encloses an $S \rightarrow I$ model.

Let us start by considering the problem of computing the probability distribution of the random variable T_{23}^* that represents the arrival time of the first infective individual in the third population. This situation is clearly different from the one we analysed in Section 6.1, since in this case the first infective traveller reaching the third population might also come from the first one, where the epidemic is well established by the time it spreads to the second population. Intuitively, populations further ahead in the line are subject to an increasing “pressure” of infective individuals coming from all populations before them, which makes differences of the form $T_{i-1,i}^* - T_{i-2,i-1}^*$, $i = 3, \dots, k-1$, smaller and smaller. This effect is shown in Figure 6.9 and Table 6.1 for simulations with ten populations of equal size and constant travel probability.

To derive an expression for the probability density function of T_{23}^* , let us again consider that the process of arrivals of infective individuals at the third population is a non-homogeneous Poisson process with time-dependent rate as in Equation (6.2), i.e. equal to the travel probability (which in this case is p_{23}) multiplied by the number of infective individuals in the second population at that time. Here, however, this number cannot take the approximated exponential form of Equation (6.4), since this would not only ignore the effect of travels, but also the fact that the epidemic in the second population was started only at time T_{12}^* by the first infective individual travelling from the first population. For these reasons, let us consider the following approximation. Given that the arrival time of the first infective individual at the second population is $T_{12}^* = t_{12}$, the number of infective individuals in the second population at time $t_{23} \geq t_{12}$ can be decomposed into two parts: (a) the endogenous growth due to infection dynamics, which starts with a single infective individual (the first traveller from the first population) at t_{12} ; (b) the exogenous growth due to travels, which also starts at t_{12} . Clearly, these two components are not independent, as the number of infective individuals that contribute to endogenous growth is also affected by travels; however, since the number of travellers is usually very small compared to the population size, these effects are negligible. Therefore, given

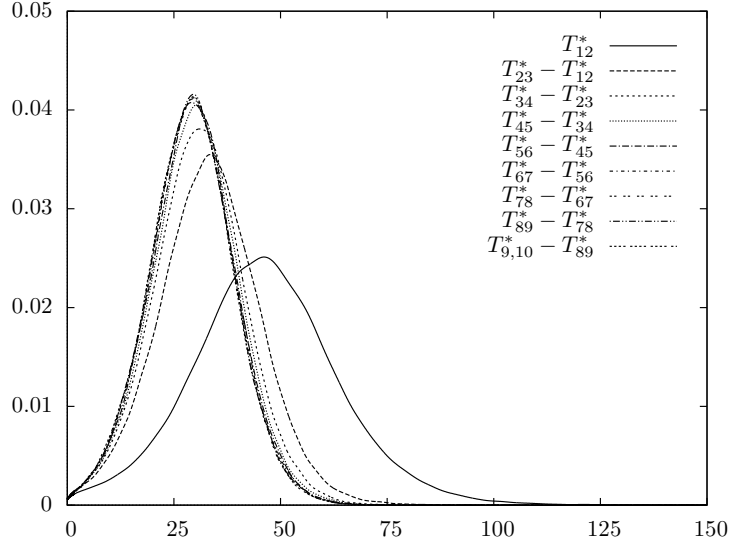


FIGURE 6.9. Gaussian kernel density estimations for T_{12}^* and differences of the form $T_{i-1,i}^* - T_{i-2,i-1}^*$, $i = 3, \dots, k-1$ obtained from 10^5 simulations of a meta-population model with ten populations arranged in a line. The infection rate is $\beta = 10^{-7}$, all populations have the same size $N_i = 10^6$, $i = 1, \dots, 10$, and all travel probabilities between adjacent populations are equal to 0.001. The main statistics are resumed in Table 6.1.

that the arrival time of the first infective individual at the second population is $T_{12}^* = t_{12}$, we define the number of infective individuals in that population at time $t_{23} \geq t_{12}$ as follows,

$$(6.20) \quad \tilde{I}_2(t_{23} | T_{12}^* = t_{12}) = I_2(t_{23} - t_{12}) + q_{12} \int_{t_{12}}^{t_{23}} I_1(\tau) d\tau, \quad t_{23} \geq t_{12},$$

where $I_1(t)$ and $I_2(t)$ are as in Equation (6.4), and q_{ij} is the probability of travelling from population i to population j and not travelling back,

$$(6.21) \quad q_{ij} = p_{ij} (1 - p_{ji}).$$

In Equation (6.20), the endogenous growth is accounted for by $I_2(t_{23} - t_{12})$, whereas exogenous growth is represented by the number of infective individuals in the first population that, from t_{12} and up to t_{23} , travelled to the second population and did not travel back.

We are now in the position to define the time-dependent rate of the non-homogeneous Poisson process describing arrivals of infective individuals at the third population; given that the arrival time of the first infective individual to the second population is $T_{12}^* = t_{12}$, we have

$$(6.22) \quad \lambda(t_{23} | T_{12}^* = t_{12}) = p_{23} \tilde{I}_2(t_{23} | T_{12}^* = t_{12}), \quad t_{23} \geq t_{12}.$$

TABLE 6.1. Mean and standard deviation of T_{12}^* and differences of the form $T_{i-1,i}^* - T_{i-2,i-1}^*$, $i = 3, \dots, k-1$ obtained from 10^5 simulations of a meta-population model with ten populations arranged in a line.

	Mean	Standard deviation
T_{12}^*	46.39165	17.22891
$T_{23}^* - T_{12}^*$	33.31884	11.90674
$T_{34}^* - T_{23}^*$	30.85396	10.76265
$T_{45}^* - T_{34}^*$	29.95288	10.32826
$T_{56}^* - T_{45}^*$	29.47931	10.15482
$T_{67}^* - T_{56}^*$	29.24084	10.11057
$T_{78}^* - T_{67}^*$	29.12777	10.03582
$T_{89}^* - T_{78}^*$	29.12826	10.03999
$T_{9,10}^* - T_{89}^*$	29.03562	10.05033

Using the results of Lemma 2.1, it is possible to compute the cumulative distribution function and the probability density function of the conditioned random variable $T_{23}^* | T_{12}^* = t_{12}$. As usual, the probability density function of T_{23}^* can be obtained by marginalization of T_{12}^* , whose probability density function was derived in Section 6.1. This computation, however, is not easily carried out and, as we shall see in Section 6.4, is not needed for our purposes.

The above result can be naturally extended to more populations; for example, the number of infective individuals at time $t_{34} \geq t_{23} \geq t_{12}$, where t_{12} and t_{23} are the time of the first arrival of an infective individual at the second and third populations, respectively, can be expressed as follows,

(6.23)

$$\begin{aligned}
& \tilde{I}_3(t_{34} | T_{12}^* = t_{12}, T_{23}^* = t_{23}) \\
&= I_3(t_{34} - t_{23}) + q_{23} \int_{t_{23}}^{t_{34}} \tilde{I}_2(\tau | T_{12}^* = t_{12}) d\tau \\
&= I_3(t_{34} - t_{23}) + q_{23} \left(\int_{t_{23}}^{t_{34}} I_2(\tau - t_{12}) d\tau + q_{12} \int_{t_{23}}^{t_{34}} \int_{t_{12}}^{\tau_2} I_1(\tau_1) d\tau_1 d\tau_2 \right),
\end{aligned}$$

from which we can immediately obtain the time-dependent rate,

$$(6.24) \quad \lambda(t_{34} | T_{12}^* = t_{12}, T_{23}^* = t_{23}) = p_{34} \tilde{I}_3(t_{34} | T_{12}^* = t_{12}, T_{23}^* = t_{23})$$

for $t_{34} \geq t_{23} \geq t_{12}$.

6.3. Distribution of the arrival time in a network of populations

So far, we have only derived expressions for the probability distribution of arrival times in the case of two or more populations arranged in a line. Of course, the topology of realistic meta-populations models is much more complex, which in turn means that our estimation method needs to be extended to take these situations into account. To understand how our method can be extended, let us start by considering the meta-population model depicted in Figure 6.10.

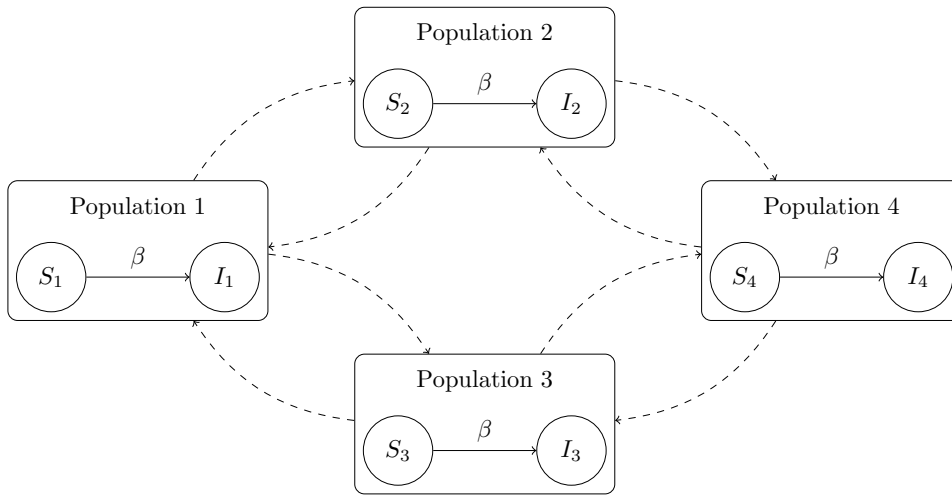


FIGURE 6.10. Meta-population model with four populations arranged in a diamond; each population encloses an $S \rightarrow I$ model. Travel probabilities are not shown for simplicity.

This model consists of four populations arranged in a diamond: the first population, which we shall again assume to host the initially infective individual, is connected to the second and third; these two are not connected to each other, but both also exchange passengers with the fourth population. The probability distribution of the time of travel of the first infective individual to either the second or third population can be easily determined by observing that both are connected to the first population only, so that the results of Section 6.1 can be applied. As for the probability distribution of the time of travel of the first infective individual to the fourth population, the situation is more complex, since this passenger might come from either the second or third population.

However, because of the additivity of Poisson processes, we can decompose the time-dependent rate of arrival of infective individual to the fourth population into two parts, one related to arrivals along the line $1 \rightarrow 2 \rightarrow 4$, and another related to arrivals along the line $1 \rightarrow 3 \rightarrow 4$. Therefore, we

have

(6.25)

$$\begin{aligned} \lambda(t_4 | T_{12}^* = t_{12}, T_{13}^* = t_{13}) &= p_{24} \tilde{I}_2(t_4 | T_{12}^* = t_{12}) \\ &\quad + p_{34} \tilde{I}_3(t_4 | T_{13}^* = t_{13}), \quad t_4 \geq \min(t_{12}, t_{13}), \end{aligned}$$

where \tilde{I}_2 and \tilde{I}_3 are given by Equation (6.20), and are equal to zero for $t_4 < t_{12}$ and $t_4 < t_{13}$, respectively.

Let us now consider the meta-population model depicted in Figure 6.11.

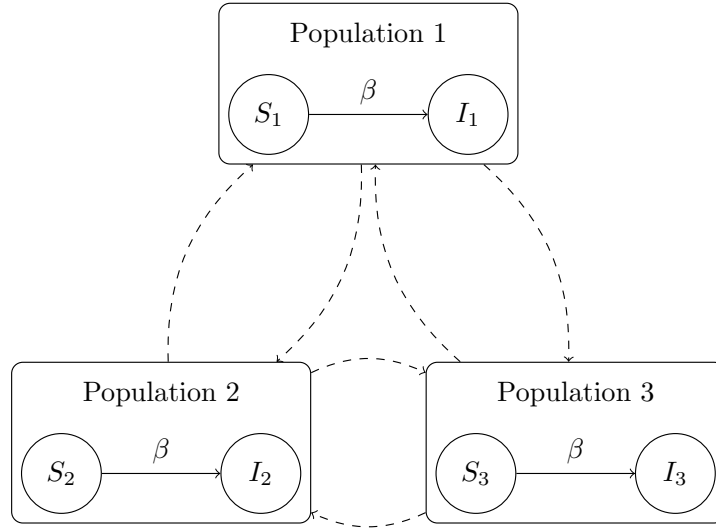


FIGURE 6.11. Meta-population model with three populations arranged in a triangle; each population encloses an $S \rightarrow I$ model. Travel probabilities are not shown for simplicity.

This model consists of three populations arranged in a triangle and all connected to each other; once again, we assume that the first population hosts the initially infective individual. In this scenario, the probability distribution of the time of travel of the first infective individual to either the second or third population cannot be easily determined: in both cases, this individual may either come from the first population, or from the remaining one. It seems that the interlinking between the populations would make it impossible to apply our estimation method.

However, this complexity is only apparent; to see why, consider a realization of the epidemic in which $T_2^* < T_3^*$, where T_i^* denotes the time of arrival of the first infective individual in population $i = 1, 2, 3$ (the case $t_2^* > t_3^*$ is analogous). Because of the ordering imposed by the arrival times, we are sure that the first infective individual cannot have arrived at the second population from the third one; therefore, we have that the probability distribution of T_2^* is equal to the one derived in Section 6.1, whereas the probability distribution of T_3^* is immediately obtained by considering that

the associated time-dependent rate can be decomposed into two parts, one related to arrivals directly from the first population, and another related to arrivals along the line $1 \rightarrow 2 \rightarrow 3$.

This reasoning can in principle be applied to networks of arbitrary complexity. It is important to understand that, even though the transportation network may be of considerable size, for estimation purposes it is generally not required to build a full model incorporating all populations, but it is sufficient to consider a subset of the original network. There are two reasons for this: (a) information about the arrival time of the first infective individual may not be available for each population, even after the epidemic has spread to most of them; (b) this kind of estimation would be most useful at the onset of an epidemic, i.e. when the disease has not yet reached all populations, so that arrival times are available only for a few of them.

6.4. Maximum-likelihood estimation of the infection rate

In this section, we briefly describe how to carry out maximum-likelihood estimation of the infection rate β from the arrival times of the first infective individuals in each population of a meta-population model with linear topology; moreover, we validate our method by means of a number of computer simulations.

Given the expressions for the time-dependent rate $\lambda(t)$ that were derived in Sections 6.1 and 6.2, we can immediately obtain the corresponding expressions for the likelihood functions. We know from Lemma 2.1 that the probability density functions of random variables representing the arrival times of the first infective individuals are of the form

$$(6.26) \quad f^*(t) = \lambda(t) e^{-\Lambda(t)}, \quad \Lambda(t) = \int_0^t \lambda(\tau) d\tau.$$

As an example, consider the time-dependent rate $\lambda(t)$ given in Equation (6.2); we have that

$$(6.27) \quad \Lambda(t) = \frac{p_{12}}{\beta} \ln \left(\frac{N_1 - 1 + e^{\beta N_1 t}}{N_1} \right)$$

and thus

$$(6.28) \quad f_{12}^*(t) = p_{12} e^{\beta N_1 t} \left(\frac{N_1 - 1 + e^{\beta N_1 t}}{N_1} \right)^{-(\beta + p_{12})/\beta}.$$

Probability density functions for other forms of the time-dependent rate $\lambda(t)$ can be obtained in the same way; since these equations easily become quite complicated, however, this is best done using a computer algebra system. From these functions we obtain the likelihood functions that, given the arrival times, the travel probabilities and the population sizes, can then be numerically maximized in β , yielding the maximum-likelihood estimate of the infection rate, denoted $\hat{\beta}$.

All computer simulations in our work were carried out using a doubly stochastic $S \rightarrow I$ model in which both infections and travels occur stochastically; this was done to understand the accuracy of the proposed estimators under more realistic conditions.

The algorithm that we developed is completely generic, and can be used with arbitrary network topologies. To improve its performance, instead of simulating directly from the associated Markov chain, we considered time to be discretized into sufficiently small time intervals of length Δ_t , and randomly generated the number of transitions of each type that occurred during each interval. Input parameters include the infection rate β , population sizes, the initial number of infective individuals in each population and the matrix of travel probabilities whose diagonal entries are determined so that each row sums to one. The main part of the algorithm is executed repeatedly while there exists at least one population to which the disease has not yet spread; it includes three main parts:

- (a) first of all, we update the arrival times of populations that received their first infective individual in the previous iteration;
- (b) secondly, we simulate travels between populations using the result of Proposition 5.1 for the number of outgoing travellers;
- (c) finally, we simulate new infections inside each population.

The output of the algorithm is a vector \mathbf{t}^* whose generic element t_i^* represent the arrival time of the first infective individual in population i . The pseudo-code is presented in Algorithm 1 at the end of this chapter.

In all simulations we considered a network with k populations arranged in a line with a constant population size of 10^6 individuals, a constant travel probability between each pair of consecutive populations equal to 0.001, and a known infection rate $\beta = 10^{-7}$.

We simulated 10^5 epidemics each for different values of k , and obtained for each simulation the maximum-likelihood estimates of the infection rate $\hat{\beta}$ using different expressions for the time-dependent rate $\lambda(t)$; these values were then used to produce Gaussian kernel density estimations whose plots are shown in the figures referenced hereafter. To improve readability, in all these plots the horizontal axis, which represents the estimated infection rate $\hat{\beta}$, has been rescaled by multiplying values by 10^6 , which means that the known infection rate $\beta = 10^{-7}$ corresponds to the value 0.1; similarly, the vertical axis has also been rescaled by multiplying values by 10^{-6} .

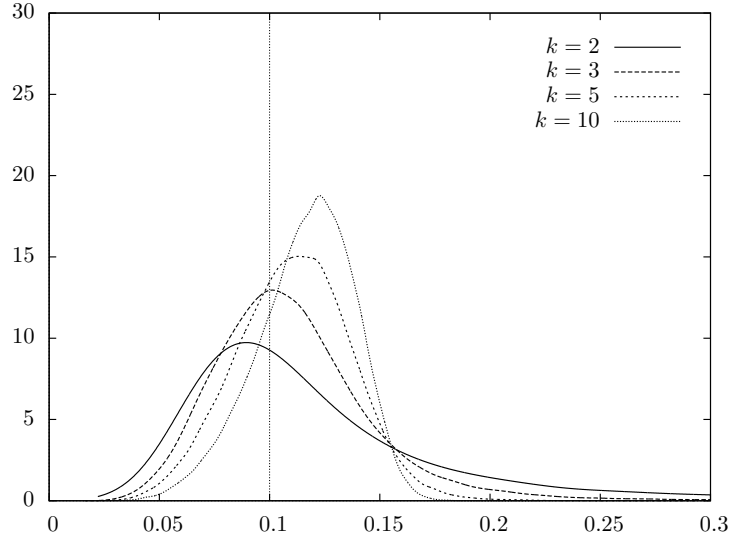


FIGURE 6.12. Gaussian kernel density estimation for the estimated infection rate $\hat{\beta}$ obtained using $\lambda(t)$ as in Equation (6.2) in meta-population models with an increasing number of populations arranged in a line; the density estimation was carried out from 10^5 simulations.

6.4.1. Estimation using Equation (6.2). Figure 6.12 shows the results obtained using $\lambda(t)$ as in Equation (6.2). Since this expression only accounts for travels between two populations, in simulations with $k > 2$ populations the estimation was carried out by assuming that the arrival time in the second of any two consecutive populations was independent and distributed identically to all others, i.e. as if all differences of the form $T_{i-1,i}^* - T_{i-2,i-1}^*$, $i = 3, \dots, k-1$, were independent and identically distributed according to Equation (6.28). Of course, this approach completely ignores the “pressure” effect described at the beginning of Section 6.2, which is why $\hat{\beta}$ shows a systematic bias towards larger values; indeed, the significant differences, shown in Figure 6.9, between the distributions of the arrival time of the first infective individual to the second population compared to others further down in the line are also reflected in the poor performance of this first estimator.

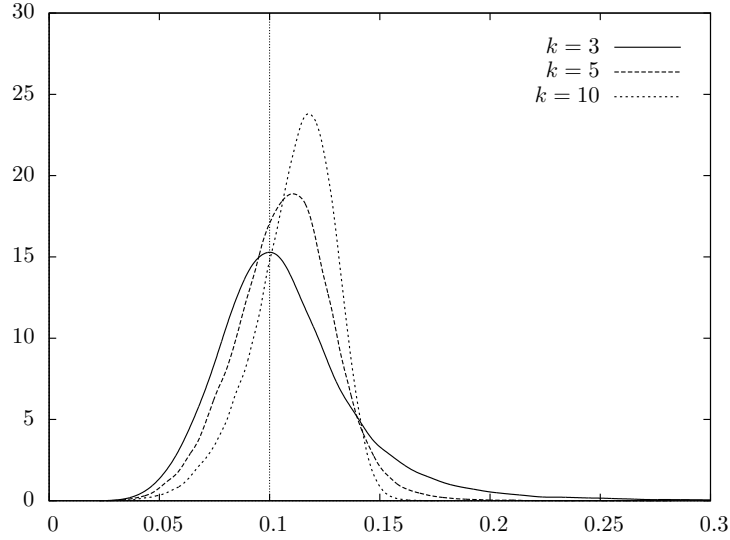


FIGURE 6.13. Gaussian kernel density estimation for the estimated infection rate $\hat{\beta}$ obtained using $\lambda(t)$ as in Equation (6.22) in meta-population models with an increasing number of populations arranged in a line; the density estimation was carried out from 10^5 simulations.

6.4.2. Estimation using Equation (6.22). Figure 6.13 shows the results obtained using $\lambda(t)$ as in Equation (6.22). Since this expression only accounts for travels between three populations, in simulations with $k > 3$ populations the estimation was again carried out by assuming that the arrival time in the third of any three consecutive populations was independent and distributed identically to all others. Moreover, for the first two populations in the line, we used $\lambda(t)$ as in Equation (6.2).

When compared to Figure 6.12, we can immediately see that the estimator obtained in this way is much more accurate, as we would expect from taking into account the difference in the distribution of the arrival time of the first infective individual to the second population compared to the third. In particular, we note that for $k = 3$ the mode of the estimator corresponds to the known value of the infection rate β .

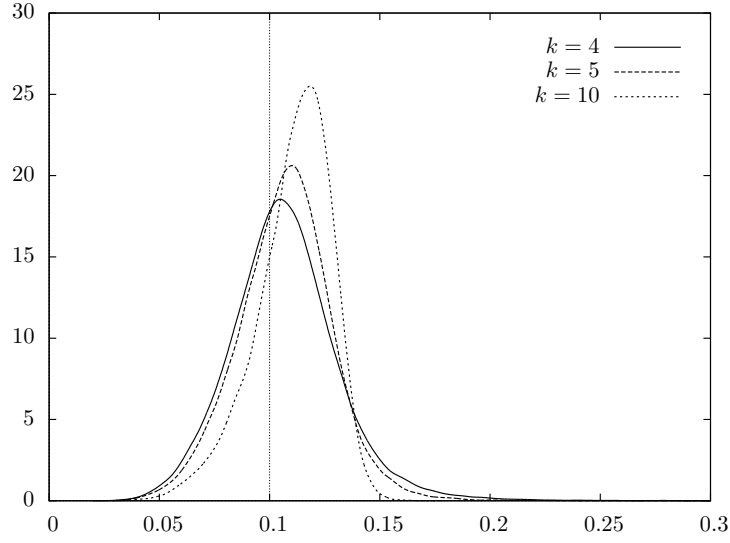


FIGURE 6.14. Gaussian kernel density estimation for the estimated infection rate $\hat{\beta}$ obtained using $\lambda(t)$ as in Equation (6.24) in meta-population models with an increasing number of populations arranged in a line; the density estimation was carried out from 10^5 simulations.

6.4.3. Estimation using Equation (6.24). Figure 6.14 shows the results obtained using $\lambda(t)$ as in Equation (6.24). Since this expression only accounts for travels between four populations, in simulations with $k > 4$ populations the estimation was again carried out by assuming that the arrival time in the fourth of any four consecutive populations was independent and distributed identically to all others. Moreover, for the first two populations in the line, we used $\lambda(t)$ as in Equation (6.2), and for the first three we used $\lambda(t)$ as in Equation (6.22).

When compared to Figure 6.13, we can notice that this estimator does not perform significantly better; this can be explained by the fact that the difference in the distribution of the arrival time of the first infective individual to the third population compared to the fourth is not as important as that between the second and third populations, as confirmed by Figure 6.9 and Table 6.1. Nonetheless, the variance of this estimator is slightly reduced, even though this small reduction comes at the price of fairly more complicated formulas.

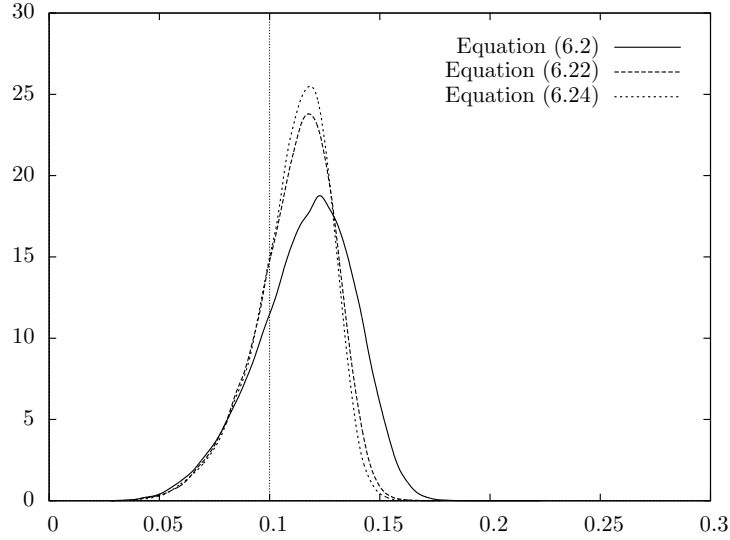


FIGURE 6.15. Comparison of the Gaussian kernel density estimations for the estimated infection rate $\hat{\beta}$ obtained using three different expressions for $\lambda(t)$ in a meta-population model with ten populations arranged in a line; density estimations were carried out from 10^5 simulations.

6.4.4. Final remarks. The results of these simulations are summarized in Figure 6.15, which shows the results obtained using the three different expressions for the time-dependent rate $\lambda(t)$ that were derived in a meta-population model with ten populations arranged in a line.

We note that all estimators tend to overestimate the infection rate β , even though this effect is particularly prominent when using $\lambda(t)$ as in Equation (6.2). As said, this systematic bias of $\hat{\beta}$ towards larger values is symptomatic of ignoring the “pressure” effect described at the beginning of Section 6.2, which is true in all three cases since the number of populations considered is higher than the one that these estimators take into account. Nonetheless, we can clearly see that accuracy improves dramatically when using the expression for the time-dependent rate $\lambda(t)$ given in Equation (6.22) instead of the one given in Equation (6.2), whereas only a small variance reduction is achieved when using $\lambda(t)$ as in Equation (6.24) instead of Equation (6.22).

Finally, we would also like to draw the reader’s attention to the fact that, as outlined at the end of Section 6.3, the number of populations that would have to be considered when estimating the infection rate β from real-world data is usually very small. In practical terms, this means that the “pressure” effect can be fully taken into account by building a complete model for these few populations, which in turn translates to greater accuracy in the inference of the infection rate β .

Algorithm 1 Stochastic $S \rightarrow I$ model with travels in discrete time**Require:**

- (1) the infection rate $\beta > 0$;
- (2) a vector \mathbf{N} with elements $N_i > 0$, $i = 1, \dots, n$, representing the initial size of population i ;
- (3) a vector \mathbf{I} with elements $I_i > 0$, $i = 1, \dots, n$, representing the initial number of infective individuals in population i ;
- (4) a matrix \mathbf{P} with elements $0 \leq p_{ij} < 1$, $i, j = 1, \dots, n$, representing the probability of travelling from population i to population j per unit time, if $i \neq j$, or the probability of remaining in population i , $p_{ii} = 1 - \sum_{j \neq i} p_{ij}$ for all $i = 1, \dots, n$.

Ensure: a vector \mathbf{t}^* with elements $t_i^* \geq 0$, $i = 1, \dots, n$, representing the time of travel of the first infective individual to population i . $\mathbf{t}^* \leftarrow [\infty, \dots, \infty]$ $t \leftarrow 0$ **while** $\exists i = 1, \dots, n. t_i^* = \infty$ **do** **for all** $i = 1, \dots, n$ **do** {update arrival times} **if** $I_i > 0 \wedge t_i^* = \infty$ **then** $t_i^* \leftarrow t \tau$ **end if** **end for** $\mathbf{I}' \leftarrow \mathbf{I}$ **for all** $i = 1, \dots, n$ **do** {simulate travels} **if** $I_i > 0$ **then** $X \sim \text{Multinomial}(I_i', \mathbf{p}_i \tau)$ **for all** $j = 1, \dots, n$ **do** **if** $j \neq i$ **then** $I_j \leftarrow I_j + X_j$ $I_i \leftarrow I_i - X_j$ $N_j \leftarrow N_j + X_j$ $N_i \leftarrow N_i - X_j$ **end if** **end for** **end if** **end for** **for all** $i = 1, \dots, n$ **do** {simulate infections} **if** $I_i > 0$ **then** $X \sim \text{Poisson}(\beta I_i (N_i - I_i) \tau)$ $I_i \leftarrow I_i + X$ **end if** **end for** $t \leftarrow t + 1$ **end while****return** \mathbf{t}^*

CHAPTER 7

Conclusions and future work

We began this thesis by presenting the main definitions and results in the field of stochastic processes (Chapter 2) and graph theory (Chapter 3) that were used later in the text. In Chapter 4, we introduced the classic deterministic and stochastic epidemic models found in the literature, and presented, in Chapter 5, two possible applications of graph theory to these models. In particular, we focused on meta-population models, which extend classic models to multiple populations by providing the coupling among them in the form of travels: we recall that, in this context, each population is represented by a vertex, and directed weighted edges connecting them encode the number of travellers per unit time in each specific direction.

In Chapter 6, we proposed a novel estimation method for the infection rate β in meta-population models that is able to infer the value of this crucial parameter from the arrival times of the first infective individuals to each population. This was made possible by the fact that the probability distributions of the arrival times depend on β . Therefore, we started by deriving the probability distributions of the time of travel of the first infective individual to the second of two populations, which we later extended to the k^{th} population in a line of k populations, and generalized to arbitrary network topologies. Finally, we described how to carry out the estimation of the infection rate using the maximum-likelihood method, and validated the accuracy of our estimators by means of a number of computer simulations.

The proposed estimation method seems to accurately infer the infection rate β even when just a few arrival times were used. Moreover, since arrival times for new diseases are commonly recorded and made available by national health services, we believe that our approach constitutes a considerable improvement over commonly used estimation approaches that, for example, try to adjust epidemic curves to sparse and inaccurate data about the number of new infective individuals over time.

For this reason, we think that the proposed estimation method is perfectly applicable to real-world situations, and we are looking forward to applying it to empirical data about the spread of influenza, which we were unfortunately unable to obtain in time for inclusion in this thesis.

As directions for future research, we believe that it would be important to generalize our method to models with more compartments, possibly allowing only individuals in specific states to travel. The model could be made more realistic by considering, for example, that susceptible individuals go through

an “exposed” state, during which the disease is latent, before becoming infective, and that they travel only if they are not infective, as originally conceived for meta-population models [32, 40].

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